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FEDERALLY-SUPPORTED HUMAN NUTRITION RESEARCH AND TRAINING

FY 1980 - FY 1982

Prepared by the

JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH
of the
Committee on Health and Medicine
and the
Committee on Food, Agriculture, and Forestry Research
Federal Coordinating Council on Science, Engineering, and Technology
Office of Science and Technology Policy
, Executive Office of the President

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INTRODUCTION

The Committee on Health and Medicine and the Committee on Food and Renewable Resources* of the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET) in the Office of Science and Technology Policy (OSTP), Executive Office of the President, established the Joint Subcommittee on Human Nutrition Research (JSHNR) to ensure that "the nutrition research efforts of the Federal agencies be mutually reinforcing." The Subcommittee was chartered on September 28, 1978. The purpose of the Subcommittee, as stated in its charter (Appendix I), "is to increase the overall effectiveness and productivity of research efforts in nutrition. In fulfilling this purpose, the Subcommittee will: (a) Improve planning, coordination, and communication among Federal agencies engaged in research on nutrition. (b) Develop and update plans for Federal research programs to meet current and future domestic and international needs for nutrition. (c) Collect, compile, and disseminate information on nutrition research. (d) Prepare reports describing activities, findings, and recommendations of the Subcommittee."

At the time of its establishment, the JSHNR consisted of representatives and alternates from the following eight Federal agencies and OSTP staff: Department of Commerce, National Oceanic and Atmospheric Administration (DOC-NOAA); Department of Defense (DOD); Department of Health and Human Services (DHHS); Federal Trade Commission (FTC); International Development Cooperative Administration, Agency for International Development (IDCA-AID); National Science Foundation (NSF); United States Department of Agriculture (USDA); and the Veterans Administration (VA). On March 11, 1980, the Subcommittee added the National Aeronautics and Space Administration (NASA) to its membership so that the human nutrition component of the NASA-manned space flight research activities be included. The FTC and NASA did not participate in the Subcommittee's activities in FY 1982 since these two agencies did not support nutrition research activities at that time.

The present report of the JSHNR has been prepared in response to the recommendation made to, and accepted by, the Director, OSTP, on page 41 of the General Accounting Office Report "Progress Made In Federal Human Nutrition Research Planning and Coordination: Some Improvements Needed" (Report CED-82-56, May 21, 1982). That recommendation stated:

We recommend that the Director of OSTP direct OSTP's Joint Subcommittee on Human Nutrition Research to develop a Federal nutrition research plan by updating and expanding its December 1980 report on federally funded human nutrition research. The process of updating the report would serve as a mechanism for achieving improved planning and coordination among the nine participating departments and agencies. In updating the report, the Subcommittee and the Federal departments and agencies should work together to develop specific goals, objectives, and strategies and to identify the responsibilities of the Federal departments and agencies and the required resources and time frames to accomplish the research goals.

* Now called the Committee on Food, Agriculture, and Forestry Research.

Dr. G. A. Keyworth, Science Advisor to the President, responded to this recommendation of the GAO report in a letter (Appendix III) to Mr. Bowsher, Comptroller General of the United States, stating that:

I concur in principle with this recommendation and perceive it to be consistent with the policies of this Administration and the intentions of the members of the Joint Subcommittee. That Subcommittee has demonstrated its commitment to effective coordination by: agreeing on a common definition of human nutrition research; describing the existing nutrition research activities and expenditures of Federal departments and agencies; identifying critical research issues; preparing reports on international nutrition research and nutrition education and professional manpower; organizing a conference to discuss research progress and research needs; and developing a common computerized data retrieval system.

These varied activities provide the groundwork for improved planning of Federal human nutrition research. It is the intention of the JSHNR to update and expand its 1980 report and to use that report as the vehicle for evolving a broad Federal nutrition research plan within which the individual agencies can develop separate plans consistent with their legislated responsibilities and missions. To the degree possible and appropriate, the Federal plan will delineate agency responsibilities and necessary resources. We agree that the process of preparing such a plan will greatly enhance Federal nutrition research programs.

The present report marks the completion of the first phase of the Subcommittee's work that focused on the identification and description of Federal human nutrition research and training programs based on the JSHNR's definition of human nutrition research, the determination of critical issues in human nutrition research for the next decade, the development of recommendations regarding these issues, and the enhancement of coordination of Federal human nutrition research programs.

This report is presented in two parts and 10 appendices.

Part I describes the accomplishments of the Subcommittee from December 1980 to December 1982 that helped to enhance the coordination and planning of nutrition research at the Federal level. These accomplishments include:

The publication of two additional reports in June, 1982--Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980's. II. International Human Nutrition Research, and III. Nutrition Education Research and Professional Needs for Nutrition Education of Professionals and the Public;

The development of the Human Nutrition Research Data Classification System; and

The organization of the first annual "Conference of Federally Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR."

Part II presents the Federal expenditures in human nutrition research for FY 1982, and includes a summary of the nutrition research programs of DHHS, USDA, VA, IDCA-AID, DOD, NSF, and DOC-NOAA for FY 1980-1982. The NASA and FTC programs are not included in this report since they were not members of the JSHNR in 1982.

Thus, this report, in conjunction with the three previous reports of the Joint Subcommittee on Human Nutrition Research, forms the foundation upon which the Federal Plan for Human Nutrition Research will be prepared.

The Subcommittee was cochaired by Mary Carter, Ph.D., Associate Administrator, Agricultural Research Service, USDA, who replaced D. Mark Hegsted, Ph.D., in September, 1982, and Artemis P. Simopoulos, M.D., Chairman, Nutrition Coordinating Committee, National Institutes of Health (NIH), DHHS, who also served as Executive Secretary. The membership of the JSHNR as of June 1983 is listed in Appendix II.

The JSHNR was terminated on June 10, 1983, and has been succeeded by the Interagency Committee on Human Nutrition Research (ICHNR) that is cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary of Agriculture, Science and Education (S&E), USDA.

USDA Orville G. Bentley
Orville G. Bentley, Ph.D.

DHHS: Artemis P. Simopoulos M.D.
Artemis P. Simopoulos, M.D.

DOC: Thomas B. Tilly
Thomas B. Tilly

DOD: David Schnakenberg
Lt. Col. David Schnakenberg, Ph.D.

IDCA-AID: Samuel G. Kahn
Samuel G. Kahn, Ph.D.

NSF: William Van B. Robertson
William Van B. Robertson, Ph.D.

VA: Victor Herbert
Victor Herbert, M.D., J.D.

I. ACCOMPLISHMENTS OF THE JOINT SUBCOMMITTEE ON HUMAN
NUTRITION RESEARCH, FY 1980-1982

The Joint Subcommittee on Human Nutrition Research (JSHNR) has taken major steps to enhance coordination and improve planning of human nutrition research at the Federal level. Its work and accomplishments have been recognized and commended by the General Accounting Office in its report, "Progress Made in Federal Human Nutrition Research Planning and Coordination; Some Improvements Needed" (Report CED-82-56, May 21, 1982, pg. 23). The report concludes:

OSTP's Joint Subcommittee on Human Nutrition Research has been a useful mechanism for getting nine departments and agencies together to share information so that they could individually do a better job in their own agencies and, more importantly, to begin establishing a base for developing a Federal nutrition research plan. We support the concept of a coordinating body within OSTP. The Joint Subcommittee has made a good start with its report on nutrition research and planned activities. Its activities, although of minimal cost to OSTP according to an OSTP official, are contributing to establishing a better system for coordinating and planning nutrition research. The subcommittee should continue to fulfill its important role in coordination and planning and reach its full potential.

As stated in the introduction, Dr. George A. Keyworth, Science Advisor to the President, in his response to this GAO Report, has stated that the JSHNR has demonstrated its commitment to effective coordination in human nutrition research at the Federal level. In addition, Congressman George E. Brown, Jr., Chairman of the House of Representatives' Subcommittee on Department Operations, Research and Foreign Agriculture, in his keynote address at the first annual "Conference of Federally Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR" (Appendix IV) stated that he was "somewhat surprised to learn that the components of Federal nutrition research management and planning were not in place prior to the establishment of the Joint Subcommittee."

Since the publication of the first JSHNR report, Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980s. I. Human Nutrition Research and Training, the JSHNR has accomplished the following major tasks directed toward further enhanced coordination of human nutrition research:

1. Publication in June 1982 of the report, Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980s: II. International Human Nutrition Research.
2. Publication in June 1982 of the report, Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980s: III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public.
3. Development of the Human Nutrition Research Data Classification System.

4. Organization of the first annual "Conference of Federally Supported Human Nutrition Research Units--an Information Exchange Activity of the JSHNR," held in Washington, D.C. on December 16-17, 1982.

REPORTS OF THE JSHNR

The three reports published by the JSHNR under the common title, Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980s, constitute the most thorough review of federally supported activities in human nutrition research ever undertaken, and collectively present an extensive review of Federal activities.

In June 1982, the JSHNR published the second and third reports of the series, i.e., II. International Human Nutrition Research and III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public.

The international report indicates that federally supported international nutrition research continues to be important in advancing nutritional science, in assisting in the solution of food and nutrition problems throughout the world, and in strengthening international relationships. The report includes a comprehensive review of Federal programs in international nutrition research, identifies critical issues in international nutrition research, and recommends maintaining and strengthening collaborative nutrition research with both developed and developing countries.

The nutrition education report indicates that nutrition education research has been successful in developing techniques for modifying the food intake of different population groups such as those at high risk for cardiovascular disease, etc., and that to be effective, nutrition education must draw from diverse disciplines, thereby requiring significant interdisciplinary cooperation. The report delineates current nutrition education research issues, presents conclusions, and makes recommendations for action if nutrition education research is to make a maximal contribution to improve the quality of life.

HUMAN NUTRITION RESEARCH DATA CLASSIFICATION SYSTEM

The Subcommittee has compiled annual tables of Federal nutrition research expenditures since FY 1979. The tables for FY 1979 through FY 1981 are reproduced in Appendix V.. Tables for FY 1982 are presented in Part II of this report.

In 1981, in order to facilitate its data collection effort in nutrition research, the JSHNR began to develop a computerized data system and compiled a list of data elements to be stored in the computer system.

The Subcommittee then developed the Human Nutrition Research Data Classification System based on the definition of human nutrition research previously developed by the Subcommittee (Appendix VI). This classification system consists of 34 categories divided into the following five major areas:

- I. Research in the Biomedical and Behavioral Sciences, including:
 - A. Research on normal nutritional requirements throughout the life cycle
 - B. Diseases and conditions
 - C. Nutrient metabolism and metabolic mechanisms at the cellular and subcellular levels
- II. Research in Food Sciences
- III. Research on Nutrition Monitoring and Surveillance of Populations
- IV. Research on Nutrition Education
- V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

This classification system, with minimal modifications, has been adopted for use by the Human Nutrition Research and Information Management (HNRIM) system. The HNRIM system was developed by the Secretaries of Agriculture and Health and Human Services with the assistance of the JSHNR in response to the congressional mandate of Section 1427 of the National Agricultural Research, Extension, and Teaching Policy Act of 1977 (7 U.S.C. 3177), as amended by Section 1425 of the National Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98). The classification system is presented in Appendix VII.

CONFERENCE OF FEDERALLY SUPPORTED HUMAN NUTRITION RESEARCH UNITS

The JSHNR, in its 1980 report, recognized the need for improved communication among the Federal agencies supporting human nutrition research. In that report, the Subcommittee made the recommendation (Recommendation 6.d) to:

Establish an annual meeting at which the Directors of the NIH Clinical Nutrition Research Units, the intramural laboratories of USDA, NIH, and FDA, the VA clinical nutrition and alcohol research programs, and the managers of DOD and NASA programs with nutrition research components will discuss research progress and future research needs. Such discussions should lead to increased coordination and collaboration among the intramural programs of USDA, NIH, FDA, DOC, NASA, DOD, and VA. Furthermore it may indicate the need for the development of joint Program Announcements and Requests for Applications and Proposals (RFAs and RFPs) by USDA, NIH, ADAMHA, FDA, NASA, and NSF. The JSHNR is uniquely qualified to determine specific needs for such joint action by cooperating agencies, and to assist in the development of mechanisms for implementation.

In response to this recommendation, the JSHNR convened an "Agenda Planning Meeting" on May 10, 1982, in Washington, D.C., to develop the agenda for

the first annual conference of the directors of the NIH supported Clinical Nutrition Research Units (CNRU); the intramural laboratories of USDA, NIH, and FDA; the VA clinical nutrition and alcohol research programs; the AID nutrition research units; and the DOD and NASA programs with nutrition research components. Approximately 40 people, from the scientific community and 8 Federal agencies, actively participated with JSHNR members in this planning meeting.

The first annual "Conference of Federally Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR" was held on December 16-17, 1982 at the National Academy of Sciences in Washington, D.C. The program and list of attendees are presented in Appendix VIII.

The Honorable George E. Brown, Jr., Chairman of the Subcommittee on Department Operations, Research, and Foreign Agriculture, U.S. House of Representatives, delivered the keynote address (Appendix IV). In his address, Congressman Brown said he was "somewhat surprised to learn that the components of Federal nutrition research management and planning were not in place prior to the establishment of the Joint Subcommittee." In describing his views of what constitutes a nutrition research plan, Congressman Brown said:

A Nutrition Research Plan developed and accepted by representatives of the broad range of disciplines which encompass the science and application of nutrition would play a major role in advancing the state-of-the-art and emphasizing to policy makers and to the public the need for sustained and continuous support. The plan I envision is not intended to be a mechanism for controlling nutrition research or dictating specific research activities which should be pursued by the implementators. Rather, the plan should serve as a guide for directing and motivating research which would achieve comprehensive nutrition goals as defined by the leaders of the numerous disciplines which encompass the science and application of nutrition. The plan must be sufficiently flexible to tap the creativity of individuals, maintain the integrity of the scientific process, and encourage centers of excellence.

The Directors of the five USDA intramural nutrition research centers, the seven NIH Clinical Nutrition Research Units, and representatives of the intramural nutrition research program of the NIH, the nutrition research program of FDA, the research programs of the DOD with nutrition components, the clinical laboratories of the VA that include nutrition research, and the two nutrition research units supported by the AID presented highlights of their research programs.

The 2-day conference concluded with a discussion of the need for continuous coordination and planning efforts by the JSHNR, and how professional scientific organizations, individual scientists, as well as foundations, may eventually be involved in the development of a National Nutrition Research Plan.

The first annual JSHNR conference provided the participants with first-hand information on the nutrition research priorities and activities

under way at the various federally supported human nutrition research centers, and thereby established a solid basis for a thorough and exciting exchange of nutrition research findings and priorities. One important point stressed by the Directors of the Centers as well as other participants was the interdependence of all components of the Federal nutrition research effort and the need to keep open the channels of communication in order to stimulate continued cooperation. The participants considered this first conference an overwhelming success and expressed a desire to participate in the second annual conference on this topic.

Proceedings of the conference are being prepared for publication in 1984 and will be made available through the National Technical Information Service (NTIS).

II. FEDERAL HUMAN NUTRITION RESEARCH, MANPOWER DEVELOPMENT, AND TRAINING ACTIVITIES, FY 1980-1982

The JSHNR carries out an annual review of Federal human nutrition research and training activities and of the level of support of these activities by all Federal agencies. The review is based upon the definition of human nutrition research developed by the Subcommittee for this purpose (Appendix VI). The FY 1982 expenditures in human nutrition research and training are presented by areas of support, i.e., extramural research, research manpower development, intramural research, research training, and research on nutrition education and information for the public, as well as by extramural and intramural support mechanisms, i.e., grants, contracts, interagency agreements, formula grants, and cooperative agreements. In addition, trends in the Federal support of human nutrition research from FY 1979-1982 are also presented by agency and area of support.

Immediately following the financial analysis of the human nutrition research expenditures are the highlights of nutrition research activities of the JSHNR member agencies, presented in decreasing order of expenditure. The highlights of the DHHS nutrition activities are followed by those of USDA, VA, IDCA-AID, DOD, NSF, and DOC-NOAA.

EXPENDITURES IN HUMAN NUTRITION RESEARCH, MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION BY FEDERAL AGENCIES

Table I indicates that in FY 1982 the Federal government spent \$207 million on human nutrition research, research training, research manpower development, and research on public information and education. The nutrition expenditures are listed in five categories of activities: extramural research, research manpower development, intramural research, research training, and research on public information and education. In order of decreasing expenditures: \$148 million (71 percent) was spent for extramural research under way in undergraduate and graduate schools of nutrition; in basic science departments of universities; in schools of medicine, dentistry, and public health; and in other schools for health professionals; and in research facilities throughout the United States and in foreign countries; \$43 million (20 percent) for intramural research in Government laboratories; \$12 million (6 percent) for research on public information and education; \$3 million (2 percent) for research training; and \$1.7 million (1 percent) for research manpower development.

Table I also indicates that of the total FY 1982 Federal expenditures for nutrition research, DHHS accounted for \$152 million (74 percent) with NIH expending \$144 million or 70 percent of all Federal expenditures; USDA expended \$46 million (22 percent); and the other agencies supported smaller, more specialized yet highly significant programs in human nutrition research that interdigitate with the programs of DHHS and USDA while at the same time fulfilling their agencies' missions.

In order to illustrate how the FY 1982 expenditures for human nutrition research compare with previous years, figures 1 and 2 present trends from 1979 through 1982 by agency and by area of support respectively.

TABLE 1

FY 1982 EXPENDITURES BY FEDERAL AGENCIES IN HUMAN NUTRITION RESEARCH,
MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION, BY AREA OF SUPPORT
(in Thousands of Dollars)

Agency	Extramural Research	Research Manpower Development	Intramural Research	Research Training	Research on Public Infor- mation and Education	Total	
DOC	304					304	0.1%
DOD	188		1,180			1,368	0.6
DHHS: NIH	129,746	1,362	7,679	3,023	2,514	144,324	70
ADAMHA	2,103	307	28	153		2,591	1
FDA	317		4,383@		692	5,392	3
CDC						0	0
HRSA	120					120	0.1
	<u>132,286</u>	<u>1,669</u>	<u>12,090</u>	<u>3,176</u>	<u>3,206</u>	<u>152,427</u>	<u>74</u>
DHHS Total							
IDCA-AID	2,602					2,602	1
NSF	1,000§					1,000§	0.5
USDA	11,438		26,563		8,357	46,358	22
VA	<u> </u>	<u> </u>	<u>3,000</u>	<u> </u>	<u>108</u>	<u>3,108</u>	<u>2</u>
TOTAL	147,818 71%	1,669 1%	42,833 20%	3,176 2%	11,671 6%	207,167 100%	100%

@ Represents 115 person-years of effort.

§ Estimated

Figure 1 illustrates that the Federal support of human nutrition research for all agencies increased from FY 1979 through FY 1981, whereas it decreased in FY 1982.

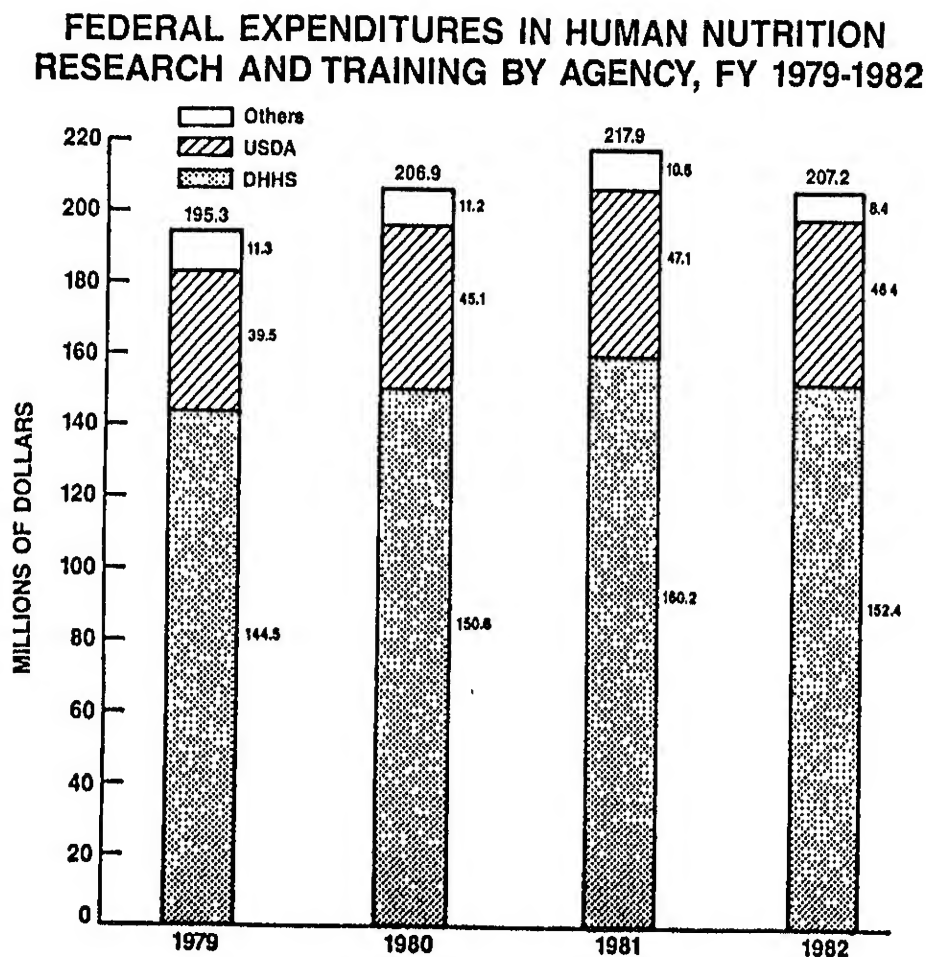


Figure 1. TRENDS IN FEDERAL SUPPORT OF HUMAN NUTRITION RESEARCH, MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION RESEARCH, BY AGENCY, FY 1979-1982.

Figure 2 illustrates that for the most part, Federal expenditures for human nutrition research in all categories of support, i.e. extramural, intramural, public information and education, research training and manpower development, increased from FY 1979 through FY 1981, and decreased in FY 1982 back to FY 1980 levels of support.

FEDERAL EXPENDITURES IN HUMAN NUTRITION RESEARCH AND TRAINING BY SUPPORT MECHANISM, FY 1979-1982

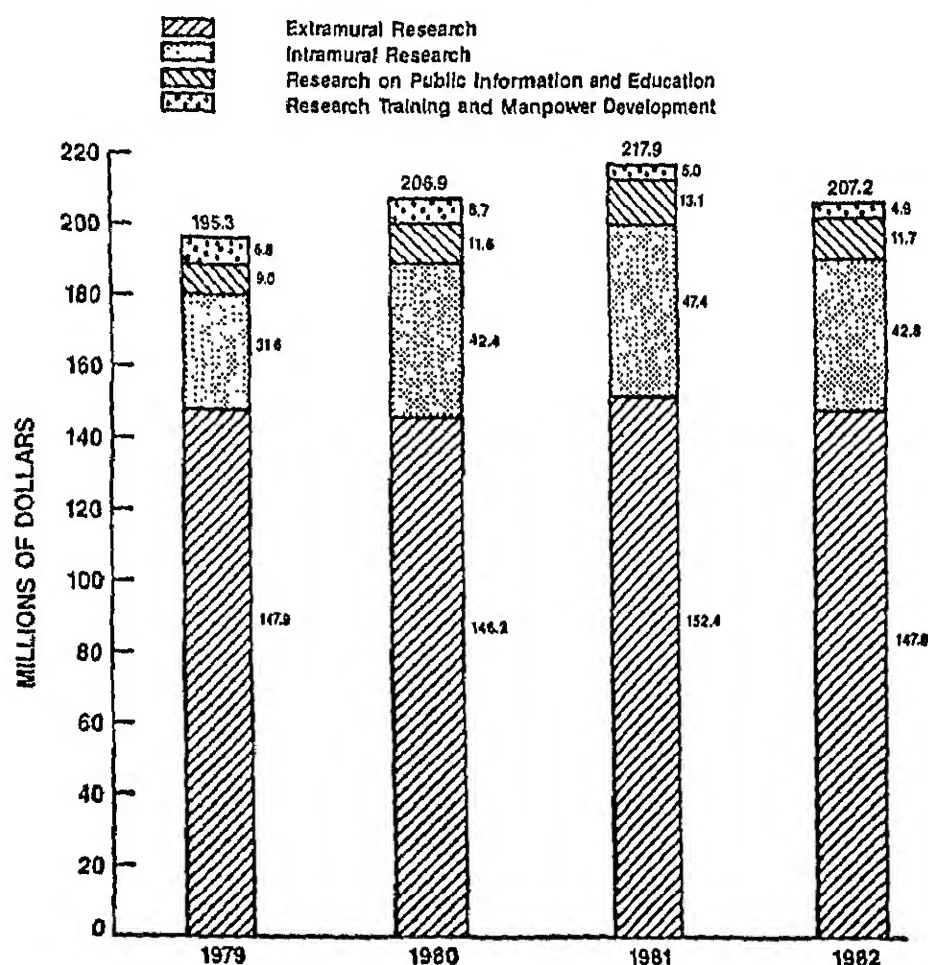


Figure 2. TRENDS IN FEDERAL SUPPORT OF HUMAN NUTRITION RESEARCH,
MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION RESEARCH,
BY AREA OF SUPPORT, FY 1979-1982.

Table II indicates the distribution of Federal human nutrition research and training expenditures for FY 1982 by support mechanism. In order of decreasing expenditures, grants (investigator initiated research) account for \$134 million (69 percent of the total); intramural research, which includes collaborative agreements, accounts for \$34 million (17 percent); while contracts account for under \$12 million (6 percent). The other 8 percent are distributed among cooperative agreements (\$8.5 million or 4 percent), formula grants (\$5 million or 3 percent), and interagency agreements (\$1.5 million or 1 percent).

TABLE II

FY 1982 HUMAN NUTRITION RESEARCH* AND TRAINING EXPENDITURES OF FEDERAL AGENCIES BY SUPPORT MECHANISM
(In Thousands of Dollars)

Department	Extramural			Intramural		Total
	Grants (competitive)	Interagency Agreements	Formula Grants	Cooperative Agreements	Intra- mural	
DOC	304					304 0.1%
DOD	65	123			1,180	1,368 0.6
DHHS: NIH	124,737	1,243			7,679	141,809 73
ADAMHA	2,563				28	2,591 1
FDA		60			4,383@	4,700 2
HRSA	120					120 0.1
DHHS Total	<u>127,420</u>	<u>1,303</u>			<u>12,090</u>	<u>149,220</u> 76
IDCA-AID	1,031					
IDCA-AID total	<u>1,090†</u>	206				2,602 1
NSF	1,000§					1,000§ 0.5
USDA	4,369	1,832	5,237	8,534	18,029	38,001 20
VA					<u>3,000</u>	<u>3,000</u> 2
TOTAL	<u>134,248</u> 69%	<u>1,509</u> 1%	<u>5,237</u> 3%	<u>8,534</u> 4%	<u>34,299</u> 17%	<u>195,495</u> 100%

* Excludes research on Public Information and Education

† Non-competitive

@ Represents 115 person-years of effort

§ Estimated

HIGHLIGHTS OF AGENCY PROGRAMS IN HUMAN NUTRITION RESEARCH

DHHS and USDA issue reports that describe their human nutrition research, manpower development, training, and education activities. The National Institutes of Health (NIH), which supports the largest Federal human nutrition research program, has issued annual reports on the NIH Program in Biomedical and Behavioral Nutrition Research and Training since 1977. The Agricultural Research Service, USDA, issued a report on Mission and Research Accomplishments in Human Nutrition Program, December 1982. The reader is referred to these reports for a detailed description of these agencies' programs. The highlights of the FY 1980-1982 nutrition research activities of DHHS and USDA are presented here, followed by overviews of the nutrition research activities of the other member agencies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

In addition to NIH, human nutrition research within DHHS is supported by the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), Food and Drug Administration (FDA) and Health Resources and Services Administration (HRSA). The National Center for Health Statistics (NCHS) and Centers for Disease Control (CDC) also carry out programs that generate data significant to the nutrition research effort of the other agencies.

In order to foster a comprehensive and effective program of nutrition research and training within DHHS, a number of agencies cosponsor various activities under the aegis of the DHHS Nutrition Research Initiative. The background and principal thrust behind the development of the Nutrition Research Initiative and those departmental activities carried out under its aegis are described below.

DHHS Nutrition Research Initiative

In April 1978, the Secretary of the Department of Health, Education and Welfare initiated a major review and reappraisal of the Department's health research activities and long-term interagency research proposals. In order to coordinate research planning and implementation, and thereby strengthen research, a steering committee consisting of representatives from the various agencies was established to define a number of health research initiatives. The initiatives were to focus on selected problem areas where mission needs of several DHHS agencies coincide with significant scientific opportunity. The health research principles approved by the Department in August 1979 were to serve as a basis in developing each initiative.

NIH was designated as the sponsoring agency to develop the Nutrition Research Initiative, and the Chairman of the NIH Nutrition Coordinating Committee was designated as the coordinator. The agencies designated as cosponsors of the initiative were: the NIH-NCC; ADAMHA; FDA; CDC; and NCHS-HANES.

The impetus to develop this initiative in nutrition stemmed from the rapidly growing scientific interest, lively public debate on the pertinence

of nutrition to particular health problems, and evolving Federal efforts to coordinate nutrition research at both policy and program levels. The purpose of the Nutrition Research Initiative is to develop within the DHHS a more comprehensive and effective program of nutrition research and training to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. A committee with members from the five agencies that conduct or support nutrition research and training was given the task of developing a cohesive program for the Department in order to best carry out this initiative in nutrition research. This committee has the following responsibilities:

- ° Review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;
- ° Coordinate research stemming from the obesity program, the CNRU's, nutrition research training and manpower development programs, and participation in OSTP's JSHNR;
- ° Provide information and advice on the nutrition research program to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;
- ° Continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and
- ° Plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

Secretary Richard L. Schweiker, the former Secretary, DHHS, inaugurated the Nutrition Research Initiative with his keynote address at the Conference on the Assessment of Nutritional Status, held at the NIH on September 16-18, 1981. This conference, as well as the second step in the implementation of the initiative, the Workshop on Body Weight Health and Longevity, are described below.

Conference on the Assessment of Nutritional Status

The objective of the conference was to highlight the current state of the art in the assessment of nutritional status. Initiated and organized by NIH-NCC, because of the high interest in the assessment of nutritional status at the bedside and in populations, the conference was planned in coordination with several PHS agencies and JSHNR members, particularly USDA and VA. The conference was cosponsored by three agencies of DHHS: NIH, CDC, and FDA. Approximately 130 scientists representing academia, industry, and government from the United States, Canada, Egypt, England, Israel, and Jamaica participated, including representatives from the members of the JSHNR. The program and participant list are presented in Appendix IX.

The conference emphasized currently available methodology, its adequacy and shortcomings, and the identification of research needed to develop

adequate methods for nutritional status assessment. Attention was given to the evaluation of the nutritional status of individuals, with emphasis on the low-birth-weight infant, the elderly, and on hospitalized patients, including surgical patients. The ability of surveys to effectively identify population segments at risk, as well as trends in the nutritional status of the entire population and specific populations were considered and extensively discussed. The utilization, by industry, of the data collected by the National Health and Nutrition Examination Survey (NHANES) was discussed also in this context.

The participants at the conference agreed that reliable methods for the assessment of nutritional status are needed in order to: determine whether or not impairment of health is the result of inadequate or inappropriate diet; establish the specific nature of any nutritional problem underlying such health impairment; provide knowledge on which to base dietary treatments for improving health; and permit evaluation of the effectiveness of nutritional treatments or interventions that may be undertaken to improve health.

The difficulties encountered in efforts to obtain reliable information about the nutritional status of both individuals and populations were emphasized frequently throughout the conference. The reasons for these difficulties include the ability of the body to adapt under adverse conditions, so that changes in biochemical or functional characteristics become evident only after substantial impairment has occurred. This requires that methods of assessment be both highly specific and highly sensitive. Furthermore, the complexity of the interactions among dietary inadequacy, disease, and personal and environmental variables makes it particularly difficult to establish whether health impairment is the result specifically of a nutritional problem or whether it is secondary to some other defect. These problems can be solved only through continuing research to expand knowledge of the patterns of biochemical, physiological, pathological, and behavioral responses to deficits or excesses of nutrients and to improve methods of applying this knowledge to individuals and groups in practical situations. The proceedings of the conference were published.*

Workshop on Body Weight, Health and Longevity

The second step in the implementation of the Nutrition Research Initiative was the Workshop on Body Weight, Health and Longevity, cosponsored by NIH-NCC and CDC, and held at the NIH on January 25-26, 1982. Representatives of other Departments also participated in this workshop, as appropriate.

Data presented at the conference indicated that, in the United States, studies based on life insurance data (i.e., the Build and Blood Pressure Study of 1959, the Build Study 1979, the Provident Life Study), the American Cancer Society Study, and other long-term studies, such as the Framingham Heart Study and the Manitoba Study, all indicate that the

* Amer. J. Clin. Nutr., 35 (Suppl):1089-1325, 1982.

weight associated with the greatest longevity tends to be below the average weight of the population under consideration, and that "slimmer is better" as long as underweight is not associated with a medical history of significant impairment and there is no evidence of calorie, protein, vitamin, or mineral deficiency.

The conference participants concluded that overweight people tend to die sooner than average weight persons; this is particularly true for those who are overweight at younger ages. This effect of overweight on mortality is delayed, so that it is not seen in short-term studies. The recent analyses of the Framingham Heart Study data emphasize that obesity is a significant independent predictor for cardiovascular disease, with smoking having an effect separate from that of overweight.

It is apparent that in addition to the age range of the population under examination, the interpretation of studies of body weight, morbidity, and mortality must be undertaken with consideration of the methods used to define overweight or relative weight; the exclusion for pre-existing morbid conditions; the length of observation of the subjects; and confounders in the analysis. The recommendations resulting from the conference are given below:

There is a need to develop an appropriate data base relating body weight by age, sex, and possibly frame size to morbidity and mortality, so as to permit the preparation of reference tables for the range of desirable body weight based on morbidity and mortality statistics. Ideally, reference data should take into account appropriate attributes (physical activity level, nature of diet, etc.), as well as possible changes in the attributes.

These changes will require new observational studies to quantify, in study populations, the relationship of such factors to morbidity and mortality. Therefore it is recommended that, at a minimum, the following data are needed for the development of a reference data table relating body weight to health and longevity:

The population studied should be representative of the healthy population to which the reference data will be applied.

Data on weight and height should be analyzed and presented separately by duration of followup, sex, and age, with age divided by decades. This procedure takes into account age-related changes in weight and permits establishment of age-related desirable weight goals.

Data on weight and height should also be expressed as W/H^2 with a median, range, and standard deviation presented for each age and sex group. Data so presented can be converted into tables relating weight and height, although questions remain regarding the validity of W/H^2 for estimating body fat in individuals outside the groups for which they were originally derived. Consequently, caution must be exercised in comparing W/H^2 between groups with standards not validated on the groups under consideration.

Efforts should be made to develop uncomplicated indices that correlate with the body's fat content better than does body mass index.

All statements regarding the ranges in which the morbidity and mortality are lowest should be based on statistically significant differences in mortality rates between the nadir of the curve and the proposed limits of the range.

The range should be broad enough to encompass subgroups whose life expectancy is known to differ because of certain life styles, such as smokers and nonsmokers, or whose socioeconomic status or other demographic characteristics contribute to differences in life expectancy. The expected differences contributed by such characteristics should be explicitly noted.

The value of indices of frame size should be assessed.

Since the latest Framingham data show that obesity is a significant independent predictor for cardiovascular disease, there is a need to:

Investigate the ways in which overweight becomes or acts as a "marker" for premature demise.

Identify the various types of obesity that are associated with specific diseases at different stages of the life cycle (e.g., upper trunk obesity with diabetes, fat cell number and hypertension in early adulthood, and fat cell size and hypertension in middle age).

Define the effect of duration of overweight in order to ascertain the specific age (how early in life) at which overweight becomes a marker for both morbidity and mortality.

In addition to the conferences, work sponsored under the Nutrition Research Initiative includes the joint PA "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior," issued by NIH and ADAMHA. This joint PA seeks to encourage new investigators in basic or clinical science disciplines to develop their research interests and capabilities in biomedical and behavioral research in order to help bridge the transition from training status to that of established investigator. ADAMHA supports research in the area of nutrition and behavior through its regular research grant programs and in specific areas of interest relevant to the National Institute of Alcohol Abuse and Alcoholism and the National Institute of Mental Health.

National Institutes of Health

The NIH Program in Biomedical and Behavioral Nutrition Research and Training is supported by the Division of Research Resources (DRR) and all 11 Institutes, namely:

National Cancer Institute (NCI)
National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Dental Research (NIDR)
National Institute of Arthritis, Diabetes, and Digestive and
Kidney Diseases (NIADDK)
National Institute of Neurological and Communicative Disorders and
Stroke (NINCDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of General Medical Sciences (NIGMS)
National Institute of Child Health and Human Development (NICHD)
National Eye Institute (NEI)
National Institute of Environmental Health Sciences (NIEHS)
National Institute on Aging (NIA)

The NIH nutrition program includes extramural and intramural research and research training, and research manpower development. The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, including departments of nutrition; and in medical, dental, and other health professional schools, including schools of public health.

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director and is advisory to the Director. The mandate of the Nutrition Coordinating Committee is to review, stimulate, and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease. Since 1977, a detailed description of the overall NIH nutrition program is published each year by the Nutrition Coordinating Committee as the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

Program Development in Nutrition Research and Training

The NCC is the focus for the review and coordination of nutrition research and training priorities, and for the development of the NIH nutrition program. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and research manpower development in nutrition need to be advanced. This is accomplished through joint program announcements (PA's) and requests for applications (RFA's) developed by the Committee and sponsored by more than one Institute. Committee representatives are also encouraged to have their individual Institutes develop program announcements, requests for applications, and requests for proposals (RFP's). Table III lists the 20 PA's, 13 RFA's and 17 RFP's in nutrition published either individually or jointly by the Institutes in FY 1980-1982, with the origin and date of each announcement, the type of announcement, and its title. These announcements cover a wide variety of research and training interests that include the assessment of nutritional status, human milk banking studies, mechanisms in food allergy, and sodium and its role in the prevention and management of hypertension. A brief summary of each announcement follows the table.

It is of interest to note that for the first time in FY 1981, a joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition--ADAMHA Special Notification for Research on Nutrition and Behavior" had the support of NIH (NCI, NIADDK, NICHD, NIA, and NIDR) and another PHS agency, ADAMHA. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Mental Health (NIMH) joined NIH in encouraging new investigators to develop their research interests and capabilities in various aspects of nutrition and behavior.

TABLE III

PA's, RFA's and RFP's In Nutrition Research And Research Training
Published In The NIH Guide For Grants and Contracts in FY 1980-1982

<u>ISSUED BY</u>	<u>DATE</u>	<u>TYPE</u>	<u>TITLE</u>
NHLBI	12/1/79	RFA	Nutritional Status and Nonrespiratory Lung Functions
NCI	1/3/80	PA	Diet, Nutrition, and Cancer Program Announcement of Research Interests in Alcohol and Cancer
NHLBI	1/7/80	RFP	Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists
NHLBI	1/7/80	RFP	Evaluation of Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists
NIDR	1/15/80	RFP	Examination of the Relationship Between Caries and Tooth Enamel Fluoride
NHLBI	1/19/80	RFP	Methodology for Estimation of Human Dietary Sodium Intake or Excretion
NICHD	1/25/80	PA	Developmental Aspects of Behavior and Nutrition
NHLBI	1/25/80	PA	Biobehavioral Approaches to the Treatment of Hypertension
NICHD	2/22/80	RFP	Longitudinal Studies of Serum Lipoprotein Changes in Users of Various Oral Contra- ceptive Preparations
NIDR	3/7/80	RFP	Studies to Identify, Isolate, Develop and Test Naturally Occurring Noncariogenic Sweeteners That May Be Used as Dietary Sucrose Substitutes

(Table III, continued)

<u>ISSUED BY</u>	<u>DATE</u>	<u>TYPE</u>	<u>TITLE</u>
NIDR	3/7/80	RFP	Research Study to Synthesize and Develop Noncariogenic Sweeteners That May Be Used as Dietary Sucrose Substitutes
NHLBI	5/13/80	RFP	Nutrition Coding Center for the Lipid Research Clinics Program and Multiple Risk Factor Intervention Trial
NIAMDD*	5/16/80	PA	Research on Diseases of the Biliary Tract and Exocrine Pancreas
NIAMDD*	6/6/80	RFA	Clinical Trial of Fluoride in Osteoporosis
NIAMDD*	6/6/80	PA	Workshop Announcement for Digestive Diseases and Nutrition
NICHD	6/6/80	RFP	The Effects of Exposure to Westernization on Infant Feeding Patterns Among Nomadic Populations
NIDR	8/29/80	PA	Research Grant Applications Sought By the National Caries Program
NICHD	1/9/81	RFP	Human Milk Banking Studies
NCI	1/26/81	RFP	Nutritional Assessment of Cancer Patients
NICHD	2/4/81	RFP	Fractionation, Identification and Characterization of Components of Colostrum and Human Milk
NCI	2/6/81	RFP	Calorimetry in Cancer Patients
NICHD	2/11/81	RFP	Clinical Studies on Human Milk
NIDR	3/6/81	RFA	National Research Service Awards for Institutional Postdoctoral Training Programs in Cariology
NIDR	3/16/81	RFP	Relationship of Dietary Intake to Caries Incidence
NHLBI	3/27/81	RFA	Demonstration and Education Research in Heart, Blood Vessel, Lung, Blood Diseases and Blood Resources

* The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) on June 29, 1981.

(Table III, continued)

<u>ISSUED BY</u>	<u>DATE</u>	<u>TYPE</u>	<u>TITLE</u>
NCC (NIA, NIADDK, NCI, NICHD, NIDR, NIAAA, NIMH)	3/27/81	Joint PA	NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior
NICHD	4/17/81	PA	Basic and Clinical Studies of Normal Development and Developmental Defects
NIADDK	4/17/81	PA	Research Interests of the Kidney Disease and Urology Program
NIDR	5/1/81	RFP	Identification of Cariogenic Elements of Foods
NCI	5/22/81	RFA	Mechanisms of Biological and Chemical Prevention of Carcinogenesis
NIAID	5/22/81	RFA	Mechanisms in Food Allergy
NHLBI	5/22/81	PA	Dietary Sodium and Its Role in the Prevention and Management of Hypertension
NIA	5/22/81	PA	Social and Behavioral Research on Aging
NIDR	9/4/81	PA	Diet and Nutrition Research
NIA	9/4/81	PA	Health and Effective Functioning in the Middle and Later Years
NIADDK NICHD NIAID	11/6/81	PA	Research Grant Support in Nutrition: Environmental and Host Factors Affecting Nutritional Requirements
NICHD	11/16/81	RFP	Long-term Effects on Infants of Hypochlor-emic Metabolic Alkalosis Resulting From Infant Formulas Deficient in Chloride (Amendment of Solicitation)
	9/17/82		
NICHD	2/26/82	PA	Successive Small-for-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome
NHLBI, NIA NIAID, NIADDK, NICHD, NIGMS	2/26/82	Joint PA	Studies on Nutritional Support of the Patient
NCI	3/26/82	RFA	The Role of Natural Inhibitors in the Prevention of Cancer

(Table III, continued)

<u>ISSUED BY</u>	<u>DATE</u>	<u>TYPE</u>	<u>TITLE</u>
NIDR	3/26/82	PA	Epidemiology of Oral Diseases in Minorities
NIAID	4/23/82	RFA	Asthma and Allergic Disease Centers
NICHD	4/23/82	PA	Adolescence Research
NIAID	4/23/82	RFA	Centers for Interdisciplinary Research On Immunologic Diseases
NHLBI	4/23/82	PA	Dietary Sodium and Its Role in The Prevention and Management of Hypertension
NIDR	4/30/82	PA	Clinical Trial of the Effect of Prenatal Fluoride Supplements in Preventing Dental Caries
NIDR	7/16/82	RFA	Fluoride and the Prevention of Root Surface Caries
NCI	8/13/82	RFA	'Accuracy' of Questionnaire Derived Historic Dietary Information
NCI	8/13/82	RFA	Epidemiologic Studies of Rare Tumors
NCI	8/13/82	RFA	Biochemical Epidemiology

Description of Announcements:

The RFA, "Nutritional Status and Nonrespiratory Lung Functions," issued by NHLBI, requested studies to elucidate the mechanisms by which nonrespiratory function of normal mature lungs are influenced by nutritional status. Areas of research supported under the announcement are nonrespiratory lung functions such as protein synthesis and degradation, (including collagen and elastin), lipid metabolism, DNA and RNA content, alterations in enzymes participating in lung defense, and energy metabolism.

The PA, "Diet, Nutrition and Cancer Program Announcement of Research Interests in Alcohol and Cancer," issued by NCI, encourages grant applications in the areas of epidemiological studies in alcohol-related cancer and basic research on alcohol effects on tumor development. Epidemiological studies combined with experimental work, are needed to delineate the steps by which alcohol consumption leads to liver cancer and to resolve the suggestion that certain beverages may predispose persons to cancer of the pancreas and rectum. Areas of basic research include: effects of alcohol on the natural history and pathogenesis of experimentally induced tumors in animals, including the effects of alcohol on immune response; influence of alcohol on the malignant potential of chemicals, oncogenic viruses and radiation; and the effects of alcohol on carcinogenesis in vivo and in vitro.

The RFP, "Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists," issued by NHLBI, solicited proposals to undertake regional training workshops for nutrition counselors to increase their knowledge and skills in three general areas: patient interviewing and nutrition counseling; assessment of characteristics related to patients and to nutrition counselors that influence nutrition education efforts; and diets in relation to hyperlipidemia, including modification for related dietary problems of obesity, diabetes, and sodium restriction. This workshop program is to test the suitability of a model workshop in various regions under the direction of personnel skilled in nutrition as related to cardiovascular disease in selected institutions or organizations.

The RFP, "Evaluation of Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists," issued by NHLBI as part of the Institute's Evaluation Program, solicited proposals for the evaluation of this program of regional workshops for nutrition counseling to determine the effectiveness, feasibility, and desirability of conducting such workshops on a regional basis. The effects of the workshop programs on the knowledge and practice of the nutrition counselors will be evaluated in order to make recommendations for improvement, and to stimulate other organizations to undertake similar activities.

The RFP, "Examination of the Relationship Between Caries and Tooth Enamel Fluoride," issued by NIDR, solicited proposals to establish and/or refine an acid etch biopsy procedure in vitro, suitable for studies in vivo, in order to examine whether a relationship exists between the subsurface fluoride content of the enamel and individual caries experience. Establishment of such a correlation would facilitate the identification of high risk individuals for participation in clinical trials and could be used to predict caries protection on smooth surfaces from new topical and/or systemic fluoride regimens.

The RFP, "Methodology for Estimation of Human Dietary Sodium Intake or Excretion," issued by NHLBI, solicited proposals for the development of improved, convenient, valid, and relatively inexpensive innovative quantitative methodology for the estimation of human dietary sodium intake or excretion. Methods to determine the sodium intake of an individual and a subgroup of individuals in a homogeneous population are useful in metabolic studies to investigate a causal relationship between sodium intake and blood pressure, and in epidemiological or preventive studies to examine the role of sodium in the etiology and treatment of high blood pressure.

The PA, "Developmental Aspects of Behavior and Nutrition," issued by NICHD, solicits grant applications for studies on the determinants of food selection and aversion, and of food intake at critical stages of the life cycle, during pregnancy, infancy, childhood, and adolescence. Studies may range from investigations of neurochemical determinants of ingestive behavior to analysis of historical, geographical, evolutionary, cultural, and psychological factors that influence ingestive behavior. Behavioral aspects of nutrition also should be amenable to study by using the methodologies of disciplines such as psychology, sociology, history and anthropology.

The PA, "Biobehavioral Approaches to the Treatment of Hypertension," issued by NHLBI, solicits grant applications for research projects to evaluate combinations of pharmacologic and non-pharmacologic therapies in the treatment of patients with diagnosed essential hypertension. Pharmacologic antihypertensive therapy has been particularly effective in reducing blood pressure in severely and moderately hypertensive patients while non-pharmacologic approaches such as exercise, diet, relaxation techniques, biofeedback, meditation, and psychotherapy have been less effective but demonstrate potential utility in maintaining pharmacologically lowered pressure. The issue of whether combinations of pharmacologic and non-pharmacologic therapies produce a synergistic effect need to be explored.

The RFP, "Longitudinal Studies of Serum Lipoprotein Changes in Users of Various Oral Contraceptive Preparations," issued by NICHD, solicited proposals to compare various commercial oral contraceptive preparations in relation to their effect on serum lipoprotein patterns, glucose tolerance, and insulin response. These parameters will be considered in a longitudinal study of women before they begin oral contraception, and during a 12- to 18-month period after they begin oral contraception.

The RFP, "Studies to Identify, Isolate, Develop and Test Naturally Occurring Noncariogenic Sweeteners That May Be Used as Dietary Sucrose Substitutes," issued by NIDR, solicited proposals for studies to recover "natural occurring" sweetening agents that must generally have sufficient sweetening power; be nontoxic; be reasonably inexpensive; have a sweetness quality comparable or similar to sucrose; be resistant to cooking temperatures; be stable at the food pH range; have "body" and or viscosity effects that contribute texture factors or smoothness in the mouth; and be noncariogenic. After identifying the potentially useful "naturally occurring" sweeteners, they are to be characterized physicochemically and evaluated under a variety of conditions of recovery, storage, and use. The characterization includes derivation of corresponding empirical and structural formulas; determination of melting point; evaluation of purity; determination of stability and solubility in aqueous solutions of various acids and alkalis at various pH levels, temperatures, and time intervals; determination of mutagenicity utilizing the Ames test; evaluation of the sensory properties of the proposed sweetener by taste panel evaluation using both sucrose and saccharin as the performance standards; and determination of possible synergistic or antagonistic action of the proposed sweetener with common food components.

The RFP, "Research Study to Synthesize and Develop Noncariogenic Sweeteners that May Be Used as Dietary Sucrose Substitutes", issued by NIDR, solicited proposals for studies to synthesize sweetening agents that must generally have sufficient sweetening power; be nontoxic; be reasonably inexpensive; have a sweetness quality comparable or similar to sucrose; be resistant to cooking temperatures; be stable at the food pH range; have "body" and or viscosity effects that contribute texture factors or smoothness in the mouth; and be noncariogenic. After identifying the potentially useful "synthesized" sweeteners, they are to be characterized physicochemically and evaluated under a variety of conditions of recovery, storage, and use. The characterization includes

derivation of corresponding empirical and structural formulas; determination of melting point evaluation of purity; determination of stability and solubility in aqueous solutions of various acids and alkalis at various pH levels, temperatures, and time intervals; determination of mutagenicity utilizing the Ames test; evaluation of the sensory properties of the proposed sweetener by taste panel evaluation using both sucrose and saccharin as the performance standards; and determination of possible synergistic or antagonistic action of the proposed sweetener with common food components.

The RFP, "Nutrition Coding Center for the Lipid Research Clinics Program and Multiple Risk Factor Intervention Trial," issued by NHLBI, solicited proposals for a nutrition coding center for the ongoing NHLBI Lipid Research Clinic (LRC) and Multiple Risk Factor Intervention Trial (MRFIT). The RFP defined the following functions of a nutrition coding center: to provide coding of the dietary recalls collected by the LRC and MRFIT programs; to maintain the nutrient data base and components of the coding system; and to provide regular training sessions and continuing education programs in dietary data collection for the LRC and MRFIT nutritionists to encourage their participation in the computerized analysis of the dietary data.

The PA, "Research on Diseases of the Biliary Tract and Exocrine Pancreas," issued by NIAMDD, solicits applications to support research and related training into the causes, diagnosis, prevention, and treatment of the diseases of the biliary tract and the exocrine pancreas. The areas of research include: multidisciplinary studies on pigment gallstone disease; studies on the effect of diet and/or drugs on biliary cholesterol saturation and plasma lipids in man and other primates; studies to discover oral and nontoxic agents that induce cholesterol unsaturated bile; and epidemiological studies to identify those individuals at greater risk for pancreatic disease, and to determine possible factors (diet, alcohol, exposure to environmental pollutants, and regional factors) that predispose certain individuals or groups of individuals to the development of pancreatitis.

The RFA, "Clinical Trial of Fluoride in Osteoporosis," issued by NIAMDD, requested applications for a clinical trial to assess the efficacy of fluoride as a therapeutic agent in treating patients with osteoporosis. Clinical data are needed to ascertain the effectiveness or toxicity of sodium fluoride at the higher dosage levels since fluoride is generally thought to stimulate osteoblastic activity and thereby increase trabecular bone mass. The primary evaluative criterion will be the incidence of fractures.

The PA, "Workshop Announcement for Digestive Diseases and Nutrition," issued by NIAMDD, requests Letters of Intent from individuals planning to submit applications for workshops or conferences to be held between October, 1981 and the end of September, 1982. An ultimate objective of the meeting is to stimulate new approaches to a problem and to encourage new investigators to become involved with a problem.

The RFP, "The Effects of Exposure to Westernization on Infant Feeding Patterns Among Nomadic Populations," issued by NICHD, solicited studies to collect information on sociodemographic and attitudinal factors, medical conditions as well as indicators of westernization, all of which may influence the decision to breast or bottle feed in Nomadic populations. The specific research objectives are to describe the trend in breast and bottle feeding in a nomadic group, that is partially undergoing a transition to a sedentary lifestyle, and to describe characteristics or possible indicators of exposure to westernization distinguishing breast from bottle feeders in both groups.

The PA, "Research Grant Applications Sought by the National Caries Program" issued by NIDR, solicits grant applications to study the etiology, pathogenesis, and prevention of dental caries in order to develop practical methods to reduce the incidence of coronal and root caries, and ultimately eliminate these major health problems. Since dental caries result from demineralization of the susceptible tooth surface by acid produced by oral flora from dietary carbohydrates, the interests of the National Caries Program focus on four strategy areas: 1) combat the responsible microbial agents, 2) increase the resistance of the tooth and host, 3) decrease caries conducive properties of the diet, and 4) improve delivery and acceptance of caries preventive measures. Two examples of areas of needed research are determining the cariostatic mechanisms of fluoride action and the influence of other dietary trace elements both on the tooth and on the cariogenic oral flora, and evaluating the impact of non-carbohydrates and of carbohydrates other than sucrose on the cariogenicity of the diet.

The RFP, "Human Milk Banking Studies," issued by NICHD, requested studies on maternal variables that may influence the composition of colostrum and human milk. The variables to be considered include: 1) maternal nutritional status, diet and post partum weight changes (including food preferences and taboos); 2) infective agents; 3) drugs and medications; 4) environmental factors such as occupational exposures; and 5) maternal behaviors such as infant feeding practices and patterns as well as maternal sociocultural factors. Studies that adapt existing methods and/or develop new methods for processing human milk are also sought. The emphasis of these studies is on procedures that assure the retention of the greatest degree of biological function of milk while rendering it safe for clinical use (both bacterial and viral contamination will be considered).

The RFP, "Nutritional Assessment of Cancer Patients," issued by NCI, solicited proposals to conduct a detailed nutritional assessment of a cohort of cancer patients. The specific issues to be addressed include the study of perturbations of a variety of nutritional parameters in the patient with advancing cancer and whether the resulting deficiencies are correctable by existing methods of nutrition intervention. The selection of the cancer categories will be based on considerations of the frequency of weight loss as a systemic effect of cancer with respect to the length of the clinical history of the tumor. Tumor categories to be studied include metastatic breast carcinoma, and/or metastatic non-small cell carcinoma of the lung. A common core of assessment techniques will be

employed in the evaluation of the patients, but a variety of additional techniques may be funded.

The RFP, "Fractionation, Identification and Characterization of Components of Colostrum and Human Milk," issued by NICHD, solicited studies to expand the knowledge base on the range of components present in human milk and colostrum as well as to characterize the physical and functional properties of previously known and newly discovered components of these fluids. Research is encouraged in at least one of the following areas: protein fractions and amino acids; lipids and essential fatty acids; factors that stimulate growth and differentiation of organ systems of the infant; and cellular fractions and humoral immunologic factors.

The RFP, "Calorimetry in Cancer Patients," issued by NCI, solicited proposals for calorimetry studies in cancer patients in order to obtain input into the design of studies that will insure the accurate and efficient evaluation of the nutritional aspects of advancing malignancy. Specific issues to be addressed include, but are not limited to: the resting caloric expenditure, the response to exercise, the response to eating, and the response to protein calorie malnutrition. The selection of cancer categories is based on considerations of the frequency of weight loss as a systemic effect of cancer in the absence of evidence of interference with gastrointestinal functions, tumor stage and the possibility of changing tumor status with treatment.

The RFP, "Clinical Studies on Human Milk," issued by NICHD, solicited clinical studies on the use of colostrum, human milk, and fractions of human milk in the nutritional management of low-birth-weight infants. The nutritional management of the low-birth-weight infants, both born prematurely and small for gestational age, attempts to achieve an acceptable rate of growth, optimum development of the immature immunologic system, and normal cognitive, behavioral, and motor development. Studies are encouraged to consider the unique appropriateness of colostrum and human milk in clinically managing the low-birth-weight infant, as well as modifying these fluids to meet the growth requirements of the infants while enabling them to receive biologically important factors found only in human milk.

The RFA, "National Research Service Awards for Institutional Postdoctoral Training Programs in Cariology," issued by NIDR, sought applications to develop methods to prevent and ultimately eliminate dental caries as a public health problem. Investigation of the diverse factors implicated in caries etiology and the development and evaluation of preventive methods necessitates participation by investigators that include organic and physical chemists, microbiologists, immunologists, pharmacologists, nutritionists, behavioral scientists, statisticians, epidemiologists, and dentists experienced in conducting clinical trials and demonstration programs. Institutions must have the faculty, facilities, and ongoing basic and clinical caries research programs to provide trainees with in-depth exposure to all of the following component subdisciplines: dental and oral anatomy and physiology; microbial etiology of caries; dietary factors in caries etiology, host immunity and susceptibility factors; use of animal models in caries research; and epidemiological

surveys and clinical trials of chemotherapeutic agents in caries research.

The RFP, "Relationship of Dietary Intake to Caries Incidence," issued by NIDR, solicited proposals to conduct a prospective study on the relationship between dietary intake patterns and the development of dental caries in a general population of school age children residing in a nonfluoridated area. Multiple, short-term, dietary intake measurements of total daily sugar consumption, total daily calories in terms of protein, fat and carbohydrate, total daily sugar consumption between meals, and total daily frequency of eating or drinking will be collected from approximately 800 school children, ages 11-13 years.

The RFA, "Demonstration and Education Research in Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources," issued by NHLBI, sought applications to help fulfill the congressional intent of Public Law 92-423 that the NHLBI establish centers "...for basic or clinical research into, training in and demonstrations of, advanced diagnostic, prevention, and treatment methods for heart, blood vessel, lung or blood diseases." These National Research and Demonstration Centers must include three essential elements: basic laboratory research, clinical investigation, and demonstration and education activities. The demonstration and education research programs are directed toward health care professionals, the community, or the general public and are staffed by scientists and physicians whose expertise may include, but is not limited to, medical disciplines, health education, epidemiology, biostatistics, and behavioral and social science. The research projects are related to the following NHLBI programs: heart and blood vessel diseases--risk factor or factors for coronary heart disease in children and/or adults including diabetes, overweight, lack of exercise, and nutrition as it affects the cardiovascular system, etc.; lung diseases and respiratory distress of the newborn, respiratory failure, etc.; and blood diseases and blood resources such as thromboembolic disorders, the hemophilias, etc.

The Joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior," issued jointly by NIH and ADAMHA, seeks to encourage new investigators in basic or clinical science disciplines to develop their research interests and capabilities in biomedical and behavioral research in order to help bridge the transition from training status to that of established investigator. The research interests of the NIH Institutes seeking applications are as follows: NIA in biomedical, social and behavioral research and research training in the areas of diet and nutrition (both basic and clinical) as these relate to the aging process and the problems and needs of the aged individual; NIADDK's Nutrition Program, Digestive Diseases Program, Hematology Program, and Diabetes, Endocrinology and Metabolism Programs in relevant nutrition research; NCI's Diet, Nutrition and Cancer Program in all areas of diet and nutrition as they may relate to cancer; NICHD in developmental aspects of nutrition, particularly in regard to reproduction, lactation, infancy, childhood and adolescence; NIDR in the relationship of nutrition to dental caries, periodontal diseases, oral soft tissue disease, and craniofacial anomalies. The ADAMHA in the area of nutrition and behavior through its regular research grant programs and in specific areas of interest relevant

to the National Institute of Alcohol Abuse and Alcoholism and the National Institute of Mental Health.

The PA, "Basic and Clinical Studies of Normal Development and Developmental Defects," issued by NICHD, encourages applications for research on the causes of congenital birth defects, due either to gene mutations or chromosomal aberrations, or to diverse agents in the internal or external environment of the developing embryo, fetus, or child. Investigations are encouraged on normal and abnormal human development during the periods prior to conception through early maturity at the basic and/or clinical level utilizing knowledge and techniques employed in disciplines such as developmental genetics, developmental biology, teratology, and developmental immunology. Nutrition, environmental chemicals, drugs, infections, maternal metabolic imbalances, ionizing radiation, as well as multifactorial insults are among the nonhereditary insults of interest as possible causes or mechanisms that produce disruptions in normal human development prior to conception and through early childhood. Also of interest are studies on immune system development during periods of malnutrition, the immunological properties of breast milk, the mechanisms that pertain to the mother's experiences with infection, the transfer of protection to the infant through breast-feeding, the events following ingestion of milk in the infant's digestive tract, and possible hazardous effects of breast-feeding.

The PA, "Research Interests of the Kidney Disease and Urology Program," issued by NIADDK, seeks applications for investigator initiated research applications and training by national research service awards, in both fundamental and clinical investigations of the mechanism and disease processes of the kidney and urinary tract. Research encouraged by the Urology Program includes studies on urolithiasis and related disorders of divalent ion metabolism (calcium, magnesium, and phosphorous) including diagnosis and treatment, physical chemistry, endocrinology, biochemistry, nutrition, transport mechanisms, calculi dissolution, and epidemiology. Also, the Chronic Renal Disease Program encourages studies on maintenance therapies for end stage kidney disease; i.e., hemodialysis, hemofiltration, peritoneal dialysis, continuous ambulatory peritoneal dialysis, as well as the role of diet in therapy, and the development and evaluation of treatments.

The RFP, "Identification of Cariogenic Elements of Foods," issued by NIDR, sought proposals to examine the effect of snack foods on caries production, salivary function, and microbial implantation in an attempt to identify and classify those elements that contribute to the cariogenicity (if any) of commonly eaten snack items. Epidemiological and dietary intake studies clearly implicate the dietary intake and the ingestion frequency of fermentable carbohydrates as an important cause in dental caries. Due to the changing eating patterns and an increase in the frequency of snacking, particularly in children who are caries susceptible, the identification of those elements rendering foods cariogenic is desirable. Food variables that have been identified in the caries process are: fermentable sugar content, retention in mouth (stickiness), texture, effect on salivary function, and effect on oral flora.

The RFA, "Mechanisms of Biological and Chemical Prevention of Carcinogenesis," issued by NCI, sought applications for studies on the mechanisms of the inhibition of carcinogenesis through the mechanisms of action of the following agents: (1) antioxidants, flavonoids, disulfiram and related compounds, nucleophiles, including cellular nucleophiles, such as glutathione and other physiological trapping agents, coumarins and other lactones; (2) vitamins, provitamins and other cofactors; (3) retinoids; (4) protease inhibitors; and (5) biological agents such as chalones, lymphokines/lymphotoxins and tumor necrosis factor. Both basic and applied studies on the mechanisms of biological and chemical prevention of carcinogenesis are to emphasize the mechanisms of anticarcinogenesis and chemoprophylaxis, as opposed to anticancer or chemotherapy. Antipromotion and/or antiprogession of carcinogenesis, as well as inhibition of initiation and fixation are components of the study.

The RFA, "Mechanisms In Food Allergy," issued by NIAID, sought applications to elucidate the basic mechanisms associated with a variety of allergic and/or adverse reactions to food. Detailed examinations of a single allergen in causing various allergic manifestations will help to define the component responsible for causing clinical reactions and to assess the diagnostic methods needed to assess specific clinical reactions. Studies are also encouraged to describe and assess precisely which allergic disorders (i.e., asthma, rhinitis, eczema, etc.) can be ascribed to allergic and/or adverse reactions to one or more food substances.

The PA, "Dietary Sodium and Its Role in the Prevention and Management of Hypertension," issued by NHLBI, encourages applications concerning a broad range of investigations including physiological, clinical, preventive, and therapeutic research regarding the role of dietary sodium in hypertension and the prevention of hypertension. Examples of needed research include studies of: the relationship between sodium and weight; the interrelationship of sodium and potassium; sodium sensitivity; salt appetite; and methods for determining sodium intake in humans. Investigations that take account of other dietary factors, caloric intake, and energy expenditure are also encouraged.

The PA "Social and Behavioral Research on Aging" issued by NIA, seeks applications in the following three broad, overlapping categories: 1) Older People in the Changing Society refers to research on age as a structural feature of society both in the population and the organization of social roles; 2) Psychological and Social Components of the Aging Process includes studies of constancy and change in social or psychological characteristics, behaviors, and environmental responses of individuals as they grow old. This category stresses the social and psychological components of aging in such concerns as nutrition, neurological and endocrine aging, and antecedents and consequences of health and health disorders generally (including social and psychological factors in the etiology of diabetes and senile dementia); and 3) Older People and Social Institutions refers to research on relations of aging individuals to the several social institutions within which they grow old, including studies of the age structure of particular institutions and how institutions can shape older people's lives and in turn be shaped by older people themselves.

The PA, "Diet and Nutrition Research," issued by NIDR, seeks applications for studies to define the influence of diet and nutrition on the growth and development of oral facial structures or repair of lesions and prevention of diseases in these structures. The goals of this research are to understand the influence of diet and nutrition on the oral and para-oral structures during all stages of life, through studies that identify and characterize the metabolic roles of nutrients and dietary conditions necessary for optimum growth, development, and aging as well as function, maintenance and repair of oral facial structures; to understand the effect of diet and nutritional deficiencies, excesses, imbalances, and other related factors on the pathogenesis and systemic sequelae of oral diseases and anomalies; and to understand and use dietary and nutritional approaches in prevention and management of oral-facial diseases and conditions.

The PA, "Health and Effective Functioning in the Middle and Later Years," issued by NIA, seeks applications for research designed to specify how psychosocial processes, interacting with biological processes, influence health and functioning in the middle and later years. One of the issues falling within this realm is that of nutrition, exercise, and sleep that includes research in the following areas: psychosocial factors influencing age related changes in food preferences, eating habits, and nutrition; cohort differences in nutrition and their consequences for health in the middle and later years of life; long-term and short-term effects on health and effective functioning of various types of exercise; psychosocial factors in etiology and therapies for age-related sleep disorders; and behavioral consequences of age-related sleep disorders.

The PA, "Research Grant Support in Nutrition: Environmental and Host Factors Affecting Nutritional Requirements," issued by NIADDK, NICHD, and NIAID, encourages studies to quantitate the dietary requirements for the essential nutrients that may be affected by age, state of human development (from fetal life to adulthood), sex, and occupation and are known to be limiting in populations living under various ecological conditions. The U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Science program has recommended that priority attention be given to studies in research areas that include: the effect of chronic infection, diarrheal disease and/or parasitism on digestion and absorption of specific nutrients or diet components; the effect of nutritional and non-nutritional dietary components on the bioavailability (absorption and utilization) of limiting essential nutrients; the determination of the functional significance of nutrients considered to be potentially limiting under a variety of dietary and ecological conditions; etc. Dietary components of special interest include energy, protein, essential amino acids, iron, zinc, vitamin A, and B₁₂. Collaborative research between U.S. investigators and investigators in Asia, or in other countries with nutritional problems similar to those in Asian countries, is particularly encouraged.

The RFP, "Long-term Effects on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride," issued by NICHD, sought proposals for a retrospective cohort study of children with a documented history of exposure to chloride deficient Neo-Mull-Soy

or Cho-Free during 1979 that resulted in metabolic alkalosis. Specific objectives of the study are: 1) to review the discharge diagnoses of metabolic alkalosis from hospitals for the period July 1978 to December 1979 using the CPHA/PAS, CHAMP, and other similar sources in order to identify children who suffered from metabolic alkalosis while exposed to the chloride deficient Neo-Mull-Soy or Cho-Free diet; 2) to identify a sample of children who were exposed to chloride deficient Neo-Mull-Soy or Cho-Free diets in 1978-1979 without metabolic hypochloremic alkalosis; 3) to identify the appropriate control groups for both groups of exposed subjects; 4) to develop a questionnaire for interviewing parents about the past and current health and development status of the children, before and after exposure to the chloride deficient formula; and 5) to identify appropriate tests for the evaluation of the children at ages 5-6 years in order to obtain data on physical growth, fine and gross motor function, dentition, and on any major deviations, including neurological impairment and mental retardation; and 6) to develop records for the abstraction of information regarding the perinatal and postnatal history and development during infancy that would include documentation of the circumstances and indications for the particular choices of infant feeding, and of the status of the children before and at the beginning of the exposure to infant feeding. This RFP resulted from the Infant Formula Act of 1980 which directs that "the Secretary of Health and Human Services shall conduct a study to determine the long-term effects on infants of hypochloremic metabolic alkalosis resulting from infant formulas deficient in chloride. The Secretary shall report the results of this study to Congress."

The PA, "Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome," issued by NICHD, seeks sources capable of performing a study of pregnant women at risk of delivering small-for-gestational age births (defined as birth weight less than 10th percentile for gestational age). The purpose of the study is to identify epidemiological risk factors which predispose mothers to have: a) repeated small-for-gestational age births and b) unexpected non-repeated small-for-gestational age births. The study will include: interviews for ascertaining nutritional and lifestyle factors from mothers in the second and third trimester; fetal growth monitoring with diagnostic ultrasound measurements at regularly specified intervals; and the collection of appropriate and uniform medical data, prenatally, perinatally and throughout the first year of life.

The PA, "Studies on Nutritional Support of the Patient," issued jointly by NHLBI, NIA, NIAID, NIADDK, NICHD, and NIGMS seeks applications on the basic and clinical research aspects of the nutritional support of patients needed in order to understand better when to institute parenteral or enteral nutrition. Results from the research will help to maximize therapy and avoid its indiscriminate use which increases medical costs, and patient risk and discomfort. Apart from its obvious therapeutic importance, parenteral and enteral nutrition provides a powerful research tool to probe and manipulate host metabolism and physiology, particularly in animal models. Research applications are being sought in the following areas: the impact of nutritional status on defense functions in the adult and developing lung (NHLBI); the specification of the nutritional

requirements of elderly patients and subsequently the enteral and parenteral nutritional support in elderly patients in acute and long-term care facilities; the assessment of the efficacy of current enteral and parenteral therapies for elderly patients (NIA); the interaction of nutrition, infection, and immunity with precise mechanisms mediating changes in immunocompetence and resistance to infection clarified, and the effects of infectious agents on nutrient metabolism elucidated (NIAID); the nutritional support of the patient as it affects the nutritional status of the whole individual (such as in cases of obesity, chronic renal failure, end-stage renal disease, anorexia nervosa and surgical trauma); nutritional status assessment methodologies; the effect of disease on nutritional requirements and the effect of nutrient intake levels on the course of specific diseases or conditions (e.g. organo-centric or disease oriented studies that primarily involve investigations related to kidney, liver, pancreas, bone and digestive diseases) (NIADDK); the nutritional support of the low-birth-weight infant and the nutritional management of certain disease states of infancy and childhood in terms of the safety and efficacy of intravenous administration of nutrients (NICHD); and studies on the metabolic and nutritional response to accidental injury, including burns (NIGMS).

The RFA, "The Role of Natural Inhibitors in the Prevention of Cancer," issued by NCI, sought applications for studies to: 1) elucidate further the protective effects of several natural inhibitors in reducing the incidence of various site specific cancers; and 2) lead to a greater understanding of the extent, or action, of several natural inhibitors in the possible cancer prevention process in humans. Natural inhibitors associated with the inhibition of carcinogenesis or with reduced cancer incidence in epidemiological investigations include vitamin C, vitamin A or its analogs, beta carotene, selenium and alpha tocopherol. The following types of studies are considered appropriate research approaches to this investigation: Case control studies of cancer patients and matched controls on the relationship of designated inhibitors with cancer incidence; cohort studies of populations that have consumed varying levels of the inhibitors; studies to examine the long-term consequences of chronic intake of various compounds in order to monitor possible adverse health effects; and risk reduction clinical trials with designated natural inhibitors administered to high risk populations free of neoplasia, or with identified precursory or pre-cancerous lesions.

The PA, "Epidemiology of Oral Diseases in Minorities," issued by NIDR, encourages applications for the support of epidemiological research related to oral health problems of racial and ethnic minority groups. Research proposed may be directed toward the identification of the patterns of occurrence, the factors and conditions, including behavioral factors, responsible for/or contributing to the following oral health problems: dental caries, in terms of the prevalence of both coronal and root caries in different age groups; periodontal diseases with studies using new methodologies for objective measurement of disease activity; congenital craniofacial anomalies (including cleft palate); and oral malignancies, other soft tissue diseases, and nutritional deficiencies with oral manifestation.

The RFA, "Asthma and Allergic Disease Centers," issued by NIAID, sought new and renewal applications for the development of Asthma and Allergic Disease Centers (AADC). The fundamental objective of the AADC program is "acceleration of the application of emerging knowledge on the immune system and from relevant biomedical sciences to clinical investigations concerned with asthma, allergic diseases, and hypersensitivity disorders." The requisite factors sought within a participating institution are quality research in: a) basic science(s), b) clinical investigation supported by adequate clinical facilities, and staff expertise in diagnosis and management of asthmatic and allergic patients, and c) access to an appropriate patient population(s) within a suitable academic/investigative setting designed to favor multidisciplinary interaction. Areas of study within the provision of this program may include those relevant to asthma and its multifactorial aspects; atopic diseases (e.g. allergic rhinitis, urticaria); pathological expressions, pathophysiologic mechanisms, and genetic factors of allergic disease and inflammation; identification, isolation and characterization of etiologic agents of allergy (e.g. drugs, foods, airborne allergens); immune mechanisms and agents of immediate hypersensitivity; immunopharmacology, immunotherapy and the development of specific pharmacological agents designed for the prevention and treatment of asthma and the other allergic diseases.

The PA, "Adolescence Research," issued by NICHD, seeks applications to support fundamental research related to biomedical and behavioral aspects of adolescence through two extramural research centers: The Center for Research for Mothers and Children (CRMC), and the Center for Population Research. One branch of the CRMC, the Clinical Nutrition and Early Development Branch (CNED), is concerned with the special nutritional requirements of the adolescent and those factors related to food choice and obesity. Since the assessment of nutritional status of adolescents is particularly difficult with food patterns often erratic, the following areas are of research interest: definition of nutrient requirements associated with the adolescent growth spurt and the onset of puberty; the development of new methods and the validation of existing methods for assessing nutritional status that are applicable to adolescence; elucidation of the cognitive, emotional and social processes involved in food choices by adolescents; investigation of the contribution of exercise and energy balance to obesity during adolescence, as well as the potential and undesirable health effects of weight reduction regimens in the obese young adolescent still undergoing physiologic maturation; and exploration of the psychological and cultural determinants of adolescent obesity through studies of techniques for modifying eating behavior and for stimulating obese adolescents to lead more active healthful lifestyles.

The RFA, "Centers for Interdisciplinary Research on Immunologic Diseases," issued by NIAID, sought applications for the participation in the ongoing program of the Centers for Interdisciplinary Research in Immunologic Diseases (CIRID). The fundamental objectives of the CIRID program is to accelerate the application of emerging knowledge on the immune system and from relevant biomedical sciences to clinical investigations concerned with asthma, allergic diseases, hypersensitivity disorders, and immunologically mediated disorders. Suitable subjects for study within the provision of this program include immunologic disorders; asthma and its

multifactorial aspect and atopic diseases (e.g. allergic, rhinitis, urticaria); identification, isolation and characterization of etiologic agents of allergy (e.g. drugs, chemicals, foods, airborne allergens); pathologic expressions, pathophysiologic mechanisms and genetic factors of allergic disease and allergic inflammation. In addition to developing broad interdisciplinary research programs in immunology, the Centers will be expected to carry out other educational or community activities.

The PA, "Dietary Sodium and Its Role in the Prevention and Management of Hypertension," issued by NHLBI, seeks applications for a broad range of investigations that include physiological, clinical, preventive, and therapeutic research, on the role of dietary sodium in hypertension and the prevention of hypertension. Examples of the research studies needed are as follows: the interrelationship of sodium and weight; sodium sensitivity; salt appetite; and methodology for determining sodium intake in humans. Investigations that take into account other dietary factors, caloric intake, and energy expenditure are encouraged.

The PA, "Clinical Trial of the Effect of Prenatal Fluoride Supplements in Preventing Dental Caries," issued by NIDR, is an attempt to determine, identify, and secure a potential study population of approximately 1,200 pregnant women, who reside in areas with less than 0.3 p.p.m. fluoride in the drinking water, in order to conduct a clinical trial of the efficacy of prenatal fluoride supplements in preventing caries in primary dentition. Caries prevalence in children whose mothers received daily fluoride supplements (1 mg F per day) during pregnancy will be compared with that of children whose mothers received placebos. Children of both groups will receive daily fluoride supplements from birth until the age of 5 years. Dental caries examinations will be conducted when the children are 3 and 5 years of age.

The RFA, "Fluoride and the Prevention of Root Surface Caries," issued by NIDR, solicited applications to investigate the effect of fluoride on the mineralization, demineralization and remineralization of artificially or naturally induced incipient lesions on root surfaces and to elucidate the anticariogenic effects of fluoride on the bacteria associated with this process. Epidemiological studies have shown that the incidence and prevalence of root surface caries is increasing in the U.S. population and that it is becoming a serious health problem. Although the etiology of root caries is not fully understood, diet, salivary properties and rate or flow of saliva, and bacterial flora in the mouth are believed to play an important role in the disease process. Evidence suggests that fluoride may be effective against root surface decay; i.e. on the basis of the effectiveness of fluoride in preventing enamel surface lesions, the variety of oral pathogens sensitive to fluoride, the histological and environmental similarities of enamel and cementum, as well as the apparent similarities in the caries process in both tissues.

The RFA, "'Accuracy' of Questionnaire Derived Historic Dietary Information," issued by NCI, sought applications for studies designed to investigate the "accuracy" and reproducibility of historical dietary information by comparing current information obtained by questioning individuals or their surrogates with actual records (data reflecting past dietary

intake) of the same individual recorded at some earlier point in time. Since nutrition has received significant emphasis as a potential etiologic or modulating factor in human carcinogenesis, it has become increasingly important to assess the degree to which dietary histories can be relied upon as substitutes for hard data on past food consumption or changes in dietary patterns. The primary focus is on the value of historical dietary information as a predictor of cancer risk since the cancer epidemiologist needs information on how well historical dietary data separates individuals into low, middle or high consumers of a specific dietary component or food group. It is also of interest to determine the "accuracy" of recall information from surrogate respondents since this procedure is necessary in the conduct of studies in cancer epidemiology where the individual of concern is deceased or unable to respond adequately. Additional variables other than elapsed time which might be investigated in such studies include the age and sex of subjects, educational level, health status, complexity of questioning, dietary variability, and the effects of "out of home" food consumption. The usefulness of special techniques to improve recall, validity of the original dietary data, its generalizeability and/or the availability of laboratory markers of past exposure should also be addressed.

The RFA, "Epidemiologic Studies of Rare Tumors," issued by NCI, sought applications for studies aimed at the elucidation of causal factors in the development of rare cancers such as malignancies of the thyroid, anus, oral canal, and anorectum; soft tissues, including heart, bone and joints; male breast; penis; and salivary gland tumors. The tumors to be investigated are not specified by this RFA. Potential etiologic factors that could be addressed include occupational/environmental exposures, genetic/familial factors, diet, drug use (therapeutic and other), cigarette smoking, behavioral factors, etc. These studies are to generate causative/etiologic hypotheses to provide clues of association; and/or to develop improved research design/methodology for the study of rare cancers. They also can provide the basis for more extended research designed to provide information on etiology and the natural history of specific rare malignant tumors or to develop studies that may provide insight into the more common tumors.

The RFA, "Biochemical Epidemiology," issued by NCI, sought applications for collaborative studies between laboratory scientists and epidemiologists in the application of a variety of sensitive and specific laboratory methods likely to facilitate epidemiologic investigations by providing better measures of exposure to initiators, promoters, anticarcinogens, and inhibitors of carcinogenesis. The usual epidemiologic techniques have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states, in measuring low levels of risk, in evaluating directly host environmental interactions, and in identifying dietary determinants of cancer. Modifying factors related to diet and nutrition have been implicated in several epithelial cancers including those of the gastrointestinal tract and reproductive organs. These types of cancers (among others) therefore might be especially suited for collaborative studies involving epidemiologists and experimentalists, including biochemists, analytical chemists, immunologists, and nutritionists.

Appropriate interaction between epidemiologic and laboratory expertise should be evident in all phases of the proposed research from planning through implementation, analysis, and reporting.

NIH Clinical Nutrition Research Units

The NIH Nutrition Coordinating Committee developed the concept of the Clinical Nutrition Research Unit (CNRU) to form the basis of a new National Program in Clinical Nutrition Research. The RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRUs)," published jointly by NCI, NIADDK, and NIA in January, 1979, led to the funding of four units in FY 1979 and an additional three units in FY 1980. These seven CNRUs continue to receive support; five units are funded by NIADDK and two by NCI.

The NIH has traditionally sponsored the individual activities that comprise a CNRU through a variety of award mechanisms, the principal ones being research grants and support for research training. The CNRU initiative, core grants for shared facilities, has become an invaluable addition, especially in promoting multidisciplinary interactions. The core grant approach also tends to ensure that a given CNRU has multiple sponsors, both Federal and non-Federal, thereby reducing the likelihood that it will become unduly dependent upon any one source for its continuing operation. Funding for educational programs and nutritional support services (patient care) are generally sought from sources other than NIH.

The specific objectives of the CNRU are:

1. To create or strengthen foci in biomedical research institutions for multidisciplinary research in clinical nutrition in order to develop new knowledge about specific nutrients in health, human development, and the prevention and treatment of disease.
2. To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition.
3. To enhance patient care and promote good health by focusing attention towards clinical nutrition and generating nutritional information for the public.

A CNRU, at a minimum, must comprise the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities.

The seven CNRUs are designed to provide the milieu for research, training, and education through coordinated effort, intellectual stimulation, and the use of shared resources. To foster such integration and to support interactions, NIH sponsors an annual meeting of the CNRU directors to discuss research progress and future research needs. To date, three annual meetings have been held.

The first annual meeting of the CNRU directors, held at NIH on December 3, 1980, was considered a tremendous success by the CNRU directors and the NIH staff in attendance. From the meeting it was evident that nutrition is a component of many research projects; courses on nutrition are being developed for use in the medical school curriculum; medical residents are being rotated through the nutrition service; the house staff is being exposed to formal and informal nutrition conferences, nutrition consultative services, and patient care activities related to nutrition; and nutrition education materials for the public are being developed.

The second annual meeting was held on December 17, 1981 at NIH. At this meeting, the importance of collaborative efforts in research methods and education activities that could be mutually reinforcing, acceptable, and useful to all seven CNRUs was emphasized. The following three areas of potential opportunity for institutional collaboration were discussed: clinical research, laboratory methods and services, and education and outreach activities. It was apparent at the second meeting that the CNRUs are effectively integrating nutrition components into many research projects, curriculum, and patient care activities, as well as in the development of nutrition education materials for the public.

The third annual meeting was held on the evening of December 15, 1982, the day preceeding the first annual Conference of Federally Supported Human Nutrition Research Units (described on pages 7-9). The meeting focused on improving communication regarding ongoing research efforts among the CNRUs. To explore a mechanism to meet this need, a computerized data retrieval system, based on the JSHNR classifications and developed under NCI sponsorship, was demonstrated. This system is designed to assist CNRU researchers to identify counterparts at other CNRUs with common research interests. The system contains information on all subprojects within each CNRU, categorized by the JSHNR classification system and by a key word index using the vocabulary of the National Library of Medicine Medical Subject Heading (MESH). The CNRU directors unanimously approved the system and its classification and coding terms and expressed their desire to use the system later this year when data entry has been completed for the final group of subprojects.

Highlights of Initiatives in Nutrition Research

A number of new areas of nutrition research have been initiated by the various Institutes, as indicated by the aforementioned PA's, RFA's and RFP's published in nutrition over the past 3 years. These announcements together with the ongoing nutrition programs have resulted in a number of significant advances. One important highlight of new initiatives in nutrition research at the NIH is the NCI's nutrition initiatives and new Chemoprevention Program. These initiatives are described below followed by the FY 1982 highlights of nutrition research described according to the 15 Special Interest Areas in Nutrition that comprise the NIH program.

The NCI has developed a number of nutrition-related initiatives with particular program relevance to a better understanding of the role of nutrient intake and nutritional status in the onset and prevention of

various forms of cancers. These initiatives include two interagency agreements; one with USDA includes pharmacokinetic studies and chronic dose studies of several forms of selenium in free-living volunteers, as well as studies of interactions between dietary beta carotene and retinol and serum beta carotene and retinol levels. The other interagency agreement is with the Finnish National Public Health Service and supports the following four studies: a randomized controlled study of beta carotene in the prevention of lung cancer; a case control study of breast cancer and nutrient intake and nutritional status with special attention to selenium, fats, and vitamins A and E; a case control study of previous nutrient intake (1960-1970) and subsequent cancers; and a case control study of pediatric cancers and maternal nutritional status as evaluated by assays for vitamins A and E, and selenium in prenatal serum.

In addition, randomized controlled dietary intervention trials are planned to investigate the effect of a low fat (20 percent) diet on breast cancer incidence in persons at high risk for developing breast cancer, as well as on the recurrence and appearance of second primary cancers in patients with stage II breast cancer.

The NCI has also developed a new program, the Chemoprevention Program, to coordinate research exploring the use of natural and synthetic agents in reducing the incidence of cancer. The goals of the program include finding ways to halt or reverse the development of cancer in people already exposed to cancer-causing agents (carcinogens) or potential carcinogens. A number of laboratory and epidemiological studies have shown that various agents can halt or reverse cancer progression in animals or reduce the incidence or risk of cancer in humans. Two groups of potential chemopreventive agents that have been identified are: naturally occurring substances found in many foods and synthetic components considered safe for clinical trials (e.g. vitamin A, beta carotene), and agents currently undergoing intensive laboratory study, but not yet ready for clinical trials such as the phenolic antioxidants, BHT and BHA, protease inhibitors, prostaglandin synthesis inhibitors, indoles and uric acid. Other dietary agents that may possibly have a preventive effect are vitamins C and E, and selenium. A complete description of the laboratory and epidemiological studies, and clinical trials that constitute the NCI's chemoprevention program is included in Appendix X.

Highlights of the NIH Nutrition Research Program

The highlights of the nutrition research program of the NIH are presented in terms of 12 scientific areas and 3 areas in nutrition education. These 15 Special Interest Areas reflect the scientific and political interest that has surrounded nutrition research in the most recent past and include in decreasing order of expenditure: Nutrition and Prevention of Disease, Research on Vitamins, Behavioral Studies in Nutrition, Child and Infant Nutrition, Nutrition and Genetics, Epidemiological Research in Nutrition, Research on Nutritional Status, Nutrition and Obesity, Nutrition Education Research, Total Parenteral and Enteral Nutrition, Maternal Nutrition, Nutrition Education for the Public, Nutrition and Aging, Nutrition Education for Professionals, and International Research in Nutrition. Similarly, the Institutes and DRR that support research in each particular area are listed with each description in decreasing order of expenditure.

Nutrition and Prevention of Disease

Research on the role of nutrition in disease prevention is supported by all NIH Institutes except NIGMS, i.e., NHLBI, NCI, NIADDK, NICHD, DRR, NIAID, NIEHS, NIA, NIDR, NEI, and NINCDS.

The definitions for prevention used by the NCC for data retrieval are as follows:

Primary prevention. Actions to promote health or undertaken prior to the development of disease; i.e., studies on nutrients to define nutritional requirements for health maintenance.

Secondary prevention Detection of disease in its early (asymptomatic) stages and intervention to arrest its expression; i.e., the use of low phenylalanine diets in children with phenylketonuria (PKU) in order to prevent mental retardation.

Tertiary prevention. Intervention after the development of a clinically manifest disease in order to reverse or arrest its progression; i.e., studies on sodium excretion for the treatment of hypertension and on low sodium diets for the treatment of the "salt sensitive" hypertensive.

Prevention of disease begins early in life and involves many factors including the metabolic, cultural and behavioral aspects of nutrition and their effects on the nutritional status of infants and children. Research continues to attempt to define nutritional requirements of the fetus and neonate in order to prevent intrauterine growth retardation and to assure optimal fetal development, and the birth and subsequent growth of healthy babies. Optimal nutritional therapy is very important for the physical, mental, and functional development, and overall health and survival of premature infants in the face of biochemical immaturity; for infants and children with inborn errors of metabolism; and those infants with certain diseases or conditions such as lactose intolerance, celiac disease, necrotizing enterocolitis, food hypersensitivity, and other diarrheal and malabsorptive conditions. This research includes studies on human milk and human milk banking in order to identify and preserve specific components of human milk and colostrum for potential use in the nutritional therapy of high-risk infants.

Studies are under way on the role of breast-feeding as a means to reduce the incidence of acute diarrhea in infants due to E. coli and Clostridium difficile. The incidence and etiology of acute gastroenteritis due to these infective agents is being assessed in breast-feeding babies and in a matched control group not breast-feeding; i.e., infections are being analyzed with regard to specific antibody titers in human milk and serum, and with regard to the presence of rotavirus, E. coli, bacterial toxins, and C. difficile in the stools of mothers and their infants who develop diarrhea.

Malnutrition and intractable diarrhea or some other infective process that exacerbates the malnourished condition is a vicious cycle. Research

on ways to rehabilitate the nutritional status of children suffering from diarrhea and the associated problems of nutrient absorption include the evaluation of the role of natural defense mechanisms of severely malnourished children. It appears that administration of fresh frozen plasma in three sequential transfusions helps to restore natural host defense mechanisms to a functional state, thereby allowing the child to fight the infection prior to any beneficial effects supplied by the nutritional therapy.

Recent studies on the cellular immune system of the normal human newborn infant have identified significant and selective maturational deficiencies. They include defects in specific cytotoxic and natural killer activities of the infant's blood. The specific regulatory mechanisms and cellular interactions need to be defined. Research in this area has specific implications for optimal infant feeding practices since infant formulas lack the immunological factors and other antimicrobial components present in breast milk and important to the prevention of neonatal infections.

Infant botulism represents the prototype of a new class of infectious diseases of infancy which involve the colonization of toxigenic spore forming bacteria in the infant gut and subsequent production of botulin toxin. This toxin produces a spectrum of diseases of varying clinical severity that can be manifest in its extreme form as crib death, also known as sudden infant death syndrome. Human milk has been shown to offer protection to the infant against toxigenic illnesses.

Nutritional therapy of infants and children with inborn errors of metabolism is designed to prevent or ameliorate the full expression of these genetic disorders. The therapy aims to minimize the patient's exposure to harmful nutrient substrates and to provide essential nutrients in required concentrations. Research on phenylketonuria (PKU), for example, has revealed that discontinuation of a low phenylalanine diet in children with PKU at age 6 was associated with higher blood phenylalanine levels (26.7 mg/dl versus 12.5 mg/dl for diet continuers) and significant differences in mean full I.Q. scores (98 versus 103 for diet continuers). Blood phenylalanine levels >20 mg/dl were associated with declining I.Q. scores. Children who remained on the low phenylalanine diet at 8 years of age showed a small but significant improvement in reading and spelling achievement tests from those children who discontinued the diet. However, improvements were not significant with the diet continued until ages 9 and 10.

Studies of maternal phenylketonuria investigate the placental transfer of phenylalanine and tyrosine in pregnant rhesus monkeys. Results suggest that 10 mg/dl of blood phenylalanine levels in the pregnant mother with PKU interferes with normal fetal central nervous system (CNS) maturation. Long-term studies to disclose what level of maternal blood phenylalanine will not damage the fetal CNS involve feeding pregnant monkeys a wide range of concentrations of L-phenylalanine in order to attain maternal mean blood phenylalanine levels of 5, 10, and 15 mg/dl throughout pregnancy. At 6 months of age, the infants are exposed to a wide variety of training, memory and discrimination paradigms in order to assess any

impairment in CNS development in terms of the maternal levels of blood phenylalanine. Additional studies on nutrition's role in the expression of various inborn errors of metabolism are described in the special interest area on "Nutrition and Genetics."

In an attempt to prevent adult obesity, studies are under way to control body weight in high risk preadolescent obese children. Investigators have demonstrated similar average weight changes after 2 years in parents and children assigned to behavioral weight control programs that are targeted to parents and children, children alone, and nonspecific weight loss targets. In terms of the treatment effects on the "maintenance" of normal weight, 100 percent of the children having parents participating maintained normal weight, while only 50 percent of the children treated alone, and 33 percent of the nonspecific control group maintained their weight. In addition, 83 percent of the children who lost weight maintained this new weight after 3 years if their parent participated in the program, while only 30 percent of those who participated alone maintained their weight. Research in this area also investigates the metabolic concomitants of obesity such as insulin resistance and glucose intolerance.

Studies of adolescents also investigate the nutrient requirements during puberty and adolescent pregnancy, as well as the problems of bulimia and anorexia nervosa. Behavioral and cultural aspects of the environment are being investigated as to their effect on the development of deleterious eating habits such as pica, food faddism, anorexia and binge eating, and the subsequent effects on nutritional status. Thus, much of the research in nutrition and prevention is concerned with the development of healthy adolescents to attain their genetic growth potential without obesity or malnutrition.

In order to understand the kind of preventive measures appropriate to the nutritional needs of the elderly, a number of studies attempt to elucidate the nutritional requirements with age, and the effect of body weight on health status in terms of longevity and disease states. Two studies examine the effect of nutritional status on immune function, i.e., the effect of protein malnutrition as well as tissue levels of a large number of nutrients on immune status.

In addition, studies of the elderly examine changes in taste and olfactory quality with age, the behavioral effects of undernutrition and aging, the effects of various living arrangements on dietary habits, stress and subsequent nutritional status, and the role of vitamin D in the prevention and treatment of osteoporosis in postmenopausal women.

Studies of osteoporosis in postmenopausal women have shown that daily doses of as little as 0.5 micrograms of 1,25 dihydroxycholecalciferol to postmenopausal women with osteoporosis increased calcium balance, and also increased trabecular bone volume and decreased bone fracture rate. These investigators have shown that after age 50, especially in postmenopausal women, plasma levels of 1,25 dihydroxycholecalciferol decrease significantly. Estradiol treatment of these women caused a 30 to 40 percent increase in circulating levels of 1,25 dihydroxycholecalciferol

and a corresponding increase in calcium absorption. Other studies have shown alpha hydroxycholecalciferol effective for the treatment of post-menopausal osteoporosis since the alpha form is readily converted by the liver into the active 1-25 dihydroxy active form.

Current knowledge about the endocrine function of vitamin D₃ metabolites, their isolation and chemical characterization has led to their widespread use to treat a variety of metabolic bone diseases such as renal osteodystrophy, hypoparathyroidism, pseudohypoparathyroidism, vitamin D resistant rickets as well as osteoporosis. In addition, measurements of the vitamin D metabolites are being used to diagnose a variety of diseases, e.g., low plasma levels of 25-hydroxycalciferol indicate intestinal malabsorption, biliary secretion failure or poor vitamin D nutritional status.

Research on another important vitamin, vitamin A, attempts to uncover its role in vision and the prevention of blindness, as well as its role in the immunocompetence of ocular tissue and its subsequent ability to respond to trauma. These studies attempt to develop animal models of xerophthalmia and keratomalacia in order to assess also the role of infection. The prevention of cataract formation is being examined through studies that modify the activity of certain enzymes such as aldose reductase, and the rate of accumulation of oxidation products such as levels of vitamins C, E, and A.

Other research on micronutrients and their role in disease prevention examines the modulating effect of trace elements such as zinc and iron on microbial virulence. Results from this research have shown that zinc deficiency not only damages cell mediated immunity in animals, but also impairs the animal's ability to control mycobacterial insult, e.g., tuberculosis infections. Protein deficiency augments this adverse effect. The animal's immune system depends more on current nutritional status, rather than a history of malnutrition indicated by reduced body weight.

New evidence on the mechanisms of microbial virulence has shown that the iron required for the growth and virulence of intracellular bacteria, such as Salmonella, is obtained from ferritin located within macrophages rather than from transferrin in blood. Also, lymphocyte uptake of the transferrin needed for their activation is inhibited by serum low density lipoproteins (LDL). Macrophages, however, can reverse the inhibitory effect of LDL by a direct effect on the LDL molecule itself.

Various nutrients, especially the amino acids, are known to affect central nervous system (CNS) development and function. A study of free lysine metabolism in the brain has shown that lysine is actively metabolized in the brain via the pipecolic acid pathway, and that some of the metabolites may have physiological functions as neurotransmitters and neuromodulators. They may therefore play an important role in certain neurological functions and conditions, i.e., sleep, sedation, schizophrenia, etc.

Other peptides present within the CNS (cholecystokinin, thyroid releasing hormone, and insulin) are involved in the regulation of feeding behavior and, therefore, in the control of body weight. Cholecystokinin (CCK) peptides are present in the brain in high concentrations, especially in

the cortex and hypothalamus. Research in sheep has shown that CCK is extremely potent in suppressing feeding behavior when injected into the cerebral ventricles, whereas injections of CCK antiserum into the cerebrospinal fluid (CSF) block satiety.

One hypothesis is that CCK is released into the brain during feeding, possibly into the ventricular system transported via the CSF, and acts on CNS receptors involved in the elicitation of satiety. Investigators are attempting to determine the sites and rates of release of CCK into the CSF during hunger and satiety as well as sites of action of brain CCK in causing satiety. Interaction of the ventromedial hypothalamus with the noradrenergic system has been proposed as a possible site of action. Suppression of feeding by CCK has also been reported to be mediated through a parenteral abdominal site.

The neuroanatomical organization of the nervous system that controls food intake and body weight regulation is being elucidated and will help to develop possible therapeutic approaches to obesity. The relationship of spontaneous obesity to monoamine function is being investigated in studies of genetically obese mice where abnormalities in the catecholaminergic system have been detected. The contribution of central catecholamines to disturbances in autonomic functions related to feeding behaviors and body weight is being examined.

Additional studies on the central nervous system development in rats seek to determine whether undernutrition early in development causes abnormalities in the synthesis or structure of gangliosides and glycoproteins in synaptic plasma membranes (SPMs). Data have shown that the offspring of rats fed either a protein-calorie deficient diet or protein deficient diet during lactation had a marked deficit of SPMs, which was greater in the forebrain and hippocampus than in the cortex or cerebellum.

The role of cobalamin in nervous tissue and its interaction with other nutrients, especially folate, is being investigated in the fruit bat (*Rousettus aegypticus*) since these animals, when made deficient, develop neuropathy without hematological cobalamin complications.

Fiber is another dietary component under investigation for its possible effect on disease prevention. Studies attempt to determine the chemical characteristics of various fiber components, to develop the appropriate methods for measuring dietary fiber, and to evaluate the effect of different forms and sources of dietary fiber components on the digestion, absorption, and bioavailability of nutrients. Some methods suggested as suitable for hydrolyzing food and fecal neutral detergent fiber (NDF) are the Saeman hydrolysis procedure as modified by Selvendren, and short periods of amylase treatment.

The various forms of fiber being studied include cellulose, xylan, pectin, corn bran, and wheat bran. Cellulose or wheat bran have been shown to decrease digestive enzyme activity in the small intestine either by dilution of the contents, or by interfering with enzyme activity. Pancreatic enzyme activity, however, increased with the ingestion of wheat bran. In terms of fiber's effect on the bioavailability of minerals, differences

may be due to variations in the fiber composition of natural fiber sources. Studies compare the effects of cellulose, xylan, pectin, and corn bran on the bioavailability of calcium, magnesium, phosphorous, iron, copper, zinc and selenium.

One study of pectin reported a decrease in B₁₂ bioavailability which, however, did not result from an interference with absorption due to calcium binding. Xylan, a bacterially digestible dietary fiber, was shown to increase liver and fecal folate levels beyond those levels provided by the diet, thereby suggesting that bacterial synthesis of folic acid was enhanced in the intestine. The effects of fiber on metabolism, therefore, may relate to the alterations in the rate of digestion and absorption of these various nutrients from the small intestine.

The possible beneficial effects of fiber in the diet are being studied in cancer patients, and in diabetic patients including pregnant women in order to test the hypothesis that a high fiber diet may reduce the diabetic's need for insulin.

Research on nutrition and prevention deals with nutrition's role in the prevention of specific diseases such as cancer, coronary heart disease, atherosclerosis, hypertension, diabetes, osteoporosis, diverticulosis, dental caries, etc. A number of studies investigate the effect of specific nutrients and other food components on the initiation, promotion and inhibition of carcinogenesis in the pancreas, liver, breast, esophagus, oral cavity, and lung.

Initiation of pancreatic carcinogenesis by coffee, and colon carcinogenesis by cycasin, methylazoxymethanol, 1-2 dimethylhydrazine, and azoxymethane is being investigated. Examinations are under way on changes in intestinal microflora and tissue enzymes, including protein kinases and phosphoproteins. Diets deficient in methyl groups are also being studied in terms of the initiation of liver and pancreas carcinogenesis in the azaserine rat model.

Other investigators have shown that ethanol acts as a carcinogen in nitrosamine carcinogenesis by increasing the metabolic activation of the target organ. Studies are under way to examine the increased risk with ethanol intake for cancer of the oral cavity, esophagus, and larynx, and the expression of carcinogenicity with liver damage.

Studies on the role of fat, especially levels of unsaturated fatty acids in the diet, attempt to provide more insight into the mechanisms of induction and promotion of cancer, as well as the simultaneous physiological effects observed with cyclopropenoid fatty acids. The murine model is being used in breast cancer studies in order to analyze the effect(s) of a polyunsaturated fatty acid (PUFA) diet on dimethylbenzanthracene (DMBA)-tumorigenesis and/or preneoplasia in BALB/c mice. The effect of PUFA promotion on the number and phenotypic properties of altered cells is being determined during latent tumor periods and in the presence of cancer promotion regimens. Saturated fat in the form of beef tallow, unsaturated fat in the form of corn oil, and a blend of fat found in the typical American diet are being tested for their effect in stimulating

mammary neoplasia after DMBA administration. The sources of fat found in the American diet can be grossly categorized into meat and poultry (40 percent), butter and dairy products (14 percent), margarine and shortenings (22 percent), salad and cooking oil (17 percent), legumes and grain products (7 percent). The blend of fat used in this study consists of beef tallow (27 percent), lard (13 percent), butter fat (14 percent), partially hydrogenated fat (22 percent), soybean oil (10 percent), peanut oil (7 percent), and corn oil (7 percent). The inhibitors of mammary carcinogenesis, propylgallate and butylated hydroxytoluene (BHT), are also being tested in terms of their effect with different types and amounts of fat. Structural or functional changes in the mammary gland will be assessed.

The inhibition of carcinogenesis is being studied using the P-450 mono-oxygenase enzyme system in the liver. Tests of chemical inhibitors and flavonoids attempt to alter the balance between activation and detoxification pathways in order that activation may be diminished. The chemopreventive agents such as flavonoids, disulfiram, ascorbic acid, selenium, glutathione, phenolic antioxidants and protease inhibitors are being examined in terms of their interactions with a variety of chemical carcinogens and the resultant chromosomal instability. Quantitative assays of the chemopreventive agents are being used to determine which agents inhibit tumor induction at specific stages, as well as the mechanism of action.

In addition, diet related cancer inhibitors such as butylated hydroxyanisole (BHA), cinnamic acids, coumarins, aromatic isothiocyanates, indoles and their derivatives are also being tested for their inhibitory activity. The levels of electrophiles available to react with DNA alkylation by N-nitroso-dimethylamine (DMN) and N-nitroso-diethylamine (DEN) in mouse lung and rat liver of BHA treated and control animals are being studied. This research attempts to unveil the mechanism by which these compounds may inhibit carcinogenesis, in an effort to develop a practical approach to the chemoprevention of cancer by low level exposures to environmental nitrosamines.

Butylated hydroxytoluene (BHT), an antioxidant added to foods at very high levels, is being studied along with glucocorticoids known to inhibit the proliferation of Type 2 cells from adenomas, accelerate the differentiation of these cells, and inhibit the toxic effects of BHT on mouse lung. In order to understand the mechanism by which BHT promotes tumors in the lung, this study will attempt to determine BHT's effect on the glucocorticoid receptors. Other studies on antioxidant action relevant to cellular processes found in carcinogenesis and tumor promotion are investigating benzopyrene metabolism and prostaglandin synthesis. Changes in the pattern of prostaglandin synthesis by the action of the antioxidant on the free radical will be determined. In addition, the interaction between the antioxidants and the electrophilic intermediates from activated esters of oncogenes *in vivo* are being ascertained in an effort to protect against mutagenesis *in cell* culture.

Folic acid is being studied for its possible role in the promotion of cancer cells back to normal and in the prevention of the progression of

early cancer cells. In one study of 47 women on combination type oral contraceptives and having abnormal pap smears, a daily regimen of folic acid significantly improved cytology scores. Deficiencies of copper, magnesium, and zinc are also being investigated in terms of their effect on cytotoxic T lymphocyte generation. Such mineral deficiencies may have an important effect on cancer promotion, and therefore amelioration of these conditions may improve cancer prevention.

A number of studies investigate the risk factors of cardiovascular disease in order to develop appropriate intervention strategies, either on a community or individual basis. Community demonstration studies have been successful in establishing coronary heart disease prevention programs in community organizational settings, churches, and schools. Various kinds of material have been developed on blood pressure control, weight control, and smoking cessation. Research continues to investigate the long-term effect of these community programs on cardiovascular disease morbidity and mortality. Attempts to modify cardiovascular disease risks are also being made through behavior programs designed for families.

Specific dietary components, such as alcohol and lipids, are being studied in terms of their effect on coronary heart disease. Results from the research on alcohol consumption indicate that the relationship of drinking behaviors to health outcomes is complex and that it is premature to recommend even moderate drinking as protection against coronary heart disease.

Studies of Greenland Eskimos revealed lower plasma lipid levels and a lower incidence of atherosclerotic diseases probably related to their diet of fish and seal. As a result of these findings, the antiatherogenic properties of the omega-3 fatty acids, found in fish and seal, are being investigated in patients with hyperlipidemia. One study includes feeding a salmon oil diet containing large amounts of these fatty acids, a vegetable oil diet high in linoleic acid, and a control diet high in saturated fat. The salmon oil diet was found to reduce plasma cholesterol and triglyceride levels more effectively than the vegetable oil, and the omega-3 fatty acid constituted up to 30 percent of the total fatty acids in each plasma lipoprotein class.

Another study in monkeys is also investigating the effects of a fish oil diet on the natural history of coronary and cerebral artery arteriosclerosis. Evidence from the study suggests that the atherosclerosis sparing effect of fish oil is due to the eicosapentanoic fatty acid's preferential incorporation into the platelet membrane phospholipid. This incorporation changes platelet function in ways favorable to diminishing atherosclerosis. These findings suggest that fish oils contain fatty acids that may be metabolically unique and potentially useful in the control of both hypercholesterolemia and hypertriglyceridemia, and therefore, in the prevention of atherosclerosis.

Additional work on atherosclerosis has revealed that cholesterol ester hydrolase (CEH) activity is lower in the mononuclear cells of patients with symptomatic atherosclerosis, as well as in those with hyperlipidemia and diabetes. The hypothesis being tested is that lower CEH activity in the intimal smooth muscle cell causes impaired cholesterol ester

hydrolytic activity and thus increases the risk of progressive atherosclerosis. It is hoped that blood monocyte CEH activity is predictive of intimal smooth muscle cell CEH activity, and therefore, those individuals at high risk may be identified prior to the occurrence of serious, atherogenic complications. Studies of CEH activity are under way in high risk patients such as those with diabetes mellitus, familial hypercholesterolemia, and a history of strokes or transient ischemic attacks.

Some investigators are testing changes in the progression or regression of atherosclerotic plaques in patients consuming the usual American diet and a cholesterol lowering diet. From studies of nonhuman primates, plaque progression and regression has been related to the rates of influx and efflux of cholesterol from the plasma. Therefore, these studies attempt to determine the cholesterol turnover rate of both free and ester cholesterol pools, the rate of cholesterol esterification, and the rate of cholesterol ester glycolysis in the diseased artery wall. Subsequently, the effect of the cholesterol lowering diet and/or drugs on these metabolic rates will also be determined.

Investigations continue to explore various methods to prevent and control hypertension, a disease that affects approximately 60 million Americans. Interim findings from one study imply that a high proportion of individuals with mild hypertension may control their blood pressure with little or no medication if weight control and sodium restriction is achieved. Biological as well as sociocultural variables related to hypertension were examined in another study of 8,000 Japanese men living in Hawaii. A multivariate analysis of this study's data indicates that obesity, age, hematocrit, heart rate, forced vital capacity, serum triglycerides and uric acid levels, cigarette smoking, and a family history of hypertension are independently associated with cross-sectional levels and longitudinal changes in hypertension.

Knowledge of specific risk factors for hypertension allows for the development of appropriate messages used in educational and behavioral modification prevention programs. Two demonstration and education research studies are exploring the possibility that dietary changes and/or relaxation training will reduce or eliminate the need for medication in hypertensives, and that paraprofessionals and nonclinic settings such as the workplace and community sites are appropriate for the non-pharmacological treatment of hypertension. A cost effective study of specific interventions to improve blood pressure control in defined populations is also under way and will provide important insight on the cost of preventive intervention strategies.

Research on the nutritional implications of kidney disease has shown that management of these patients requires restrictions of sodium, potassium, phosphate and fluids. Progressive loss of kidney function changes additional endocrine and metabolic functions. For example, with advanced renal failure, vitamin D₃ is not converted to 1,25 dihydroxycholecalciferol D₃ and therefore calcium homeostasis is affected, resulting in uremic bone disease. In addition, these patients experience insulin resistance and therefore require higher levels of insulin to achieve control of glucose levels; and have altered carbohydrate, fat, and protein

metabolism, and differences in vitamin requirements. A variety of projects are devoted to either the basic mechanistic understanding of these differences in metabolism or the practical issues of patient requirements.

Nutritional therapy for the treatment of patients with chronic renal failure has important implications for reducing the frequency and perhaps the need for dialysis. Low protein diets have been shown to maintain non-dialyzed chronically uremic patients relatively free of uremic symptoms. Two low protein diets, namely, one providing .55-.60 grams/kg/day of high quality protein and one providing 20 grams/day of varied quality protein as well as 20.7 grams/day of nine essential amino acids, have been successful in maintaining near normal serum protein levels and anthropometric measurements. They also appear useful for extended periods of time.

Patients with end-stage renal disease but with some residual renal function, also have been successfully maintained with low protein diets coupled with reduced frequency dialysis. For example, patients either on a diet of 0.96 ± 0.12 grams/kg/day of protein at 65 percent high biological value, or on a diet of 0.4 grams/kg/day of protein at 40 percent high biological value plus 10 grams/day of essential amino acids, maintained a positive nitrogen balance for 2 to 6 months, had lower concentrations of blood urea nitrogen, normal serum protein levels and normal nerve conduction velocities. More studies will be conducted in this area since successful rehabilitation of these patients with nutritional therapy coupled with reduced dialysis frequency would be a considerable cost savings.

Other research on chronic renal failure is under way in a rat model in order to observe the possible consequences of a high phosphate diet on the loss of kidney function. Rats on the higher phosphate diets were shown to have higher serum calcium levels, and more calcification and adverse histological changes in the kidney. This research lends support to the hypothesis that higher phosphate diets accelerate kidney function loss through calcification in the cortical tubular cells, basement membranes, and interstitium, occurring in the course of renal failure.

Tooth decay affects most children as early as primary teeth erupt. By 11 years of age, the average American child has three permanent teeth attacked by caries, while by 17 years of age, eleven permanent teeth have decayed, been filled, or are missing. Prevention efforts are aimed at making teeth less susceptible to caries by use of fluorides and by decreasing the frequency of sugary foods.

Research on nutrition's role in the prevention of dental caries, therefore, includes studies to develop noncariogenic sweeteners. In recent years, plant derived sweeteners used by native populations in other countries have shown promise for use in the U.S. Scientists have isolated, purified, characterized and subjected to a taste panel all the sweet principles from Stevia rebaudiana, a plant native to Paraguay. Extracts from this plant are used in Japan in commercially produced foods such as chewing gum, soft drinks, sauces and pickles. Other alternate sweeteners used by native populations are under study from the

following plants: Hydrangea thumbergia, native to Japan; Mormodica gros-veneri, native to Southern China; and Lippia dulcis, native to Mexico. A number of tests for potential health hazards of these sweeteners will be required before they are released in the market place.

In addition to sugar, other factors known to modulate the cariogenicity of foods include eating frequency, presence of cariostatic agents, food texture, food stickiness, induction of salivation, etc. To examine these factors, scientists have developed a highly reproducible rat model that provides by intubation essential nutrition as well as 17 daily snack foods at hourly intervals. The cariogenic potential index (CPI) of a food is the ratio of the caries scores resulting from the ingestion of the test food compared to powdered sucrose. The CPI of foods tends to increase with increasing sugar content, as in the case of breakfast cereals. However, some results indicate that the elements in food that give rise to an increased CPI are not fully understood. This rat model shows great promise in examining the complex relationship of those factors important to the cariogenicity of a particular food. Because the test food is the only food that comes into contact with the rat's oral cavity, this rat model can be used to measure the relationship of a food's CPI value and other parameters such as the salivary enzyme activities and the presence or absence of immune factors.

Research on Vitamins

Research on vitamins includes studies to determine their requirements in specific age groups, particularly in the fetus, neonate, and the elderly; the metabolic processes in normal as well as transformed cells; and their interrelationships in the intact organism. In FY 1982, NCI, NIADDK, DRR, NICHD, NEI, NHLBI, NINCDS, NIDR, and NIA supported research in this area.

A number of studies are investigating the role of vitamin A in the differentiation of epithelial tissue and in fetal growth and development. Dietary requirements of vitamin A during pregnancy and lactation have not been thoroughly determined and few data exist on fetal and neonatal requirements. It is likely that vitamin A requirements vary with protein intake when this intake is inadequate. Studies are under way to evaluate the hepatic, renal and gastrointestinal controls of the mother's metabolism of vitamin A and related compounds; to characterize placental transport, especially of retinol when vitamin A intake is low or excessive; and to examine the effect of supplemental doses of vitamin A on placental transport, fetal metabolism and the trans-placental retinol transport system. Data indicate that placental transport of vitamin A decreases with excessive maternal intake or when maternal stores are high, and increases when stores are low. Examination of vitamin A metabolism in the maternal-fetal-neonatal unit must include examination of the effects of protein intake since vitamin A transport, storage and utilization all are influenced by protein intake. Vitamin A is also being examined for its effect on the development of teeth and bones since deprivation of the vitamin in rats leads to increased caries development.

In terms of the molecular mechanisms of vitamin A, intracellular binding proteins for retinol and retinoic acid have recently been characterized.

Retinol and retinoic acid have been shown to influence genomic expression in vivo by activation as well as suppression of the genome; the binding protein for retinol (CRBP) delivers retinol to the nuclei of rat liver cells where it associates with the chromatin. The protein does not remain bound. The retinol-chromatin interaction presumably affects the genomic expression underlying cell differentiation.

Investigations on the teratogenic effects of excess vitamin A and zinc deficiency in rats have revealed a high incidence of fetal malformations from either treatment, but no interaction between them. Brain deformities resulted under both conditions; excess vitamin A resulted in a higher incidence of fetal eye and palate anomalies than the zinc deficiency, but had no effect on DNA synthesis. Zinc deficiency caused a higher incidence of lung and tail malformations and a low uptake of H^3 thymidine into embryonic DNA.

A major focus of vitamin A metabolism is on its role in the visual process and in the integrity of ocular epithelium. The enzymatic mechanisms by which 11-cis-retinaldehyde is formed from all-trans retinal and bound to protein in the formation of rhodopsin is under investigation in photoreceptor cells. Other studies are looking at the effect of vitamin A deficiency alone as well as with calcium and zinc deficiencies on dark adaptation; the role of specific ocular retinol binding proteins in the intracellular transport of retinoids between the retinal pigment epithelium and rod outer segments; the effect of aging on the efficiency of vitamin A utilization for rhodopsin formation; vitamin A's role in the corneal response to infection and trauma, particularly as this relates to corneal melting and keratomalacia, the prevalence of xerophthalmia and keratomalacia and associated risk factors for their development in India; and a new approach to the assessment of vitamin A status in children with and without various degrees of protein-calorie malnutrition.

Studies of the modulation, mediation, prevention and treatment of cancer with vitamin A and its retinoid analogs comprise a large portion of research in this area. A number of animal models are being used to investigate the effect of moderately high and marginally low vitamin A supplementation on the initiation and promotion of carcinomatous and benign mammary tumors in rats treated with dimethylbenzanthracene (DMBA) and methylnitrosourea (MNU); the effect of retinoids and selenium on the inhibition of bladder carcinogens; and the effects of retinoid and difluoromethylornithine on cancer incidence, latency, and tumor number.

In order to understand the molecular mechanisms of retinoids that alter intracellular events resulting in abnormalities in cell growth and carcinogenesis, the ability of retinoids to inhibit ornithine decarboxylase induction and increase RNA synthesis is being evaluated in isolated nuclei from proliferating and retinol arrested cells. The possibility that retinoids may act as corticosteroids and inhibit collagenase production at some level of mRNA transcription is being tested using phorbol myristate acetate treated synovial fibroblasts from rabbits. Other studies consider the antitumor activity of retinoids in terms of the stimulatory effects on the immune system; retinoic acid is thought to promote lymphoid differentiation in the retinoid-mediated neutralization

of tumor promotion by phorbol ester. The mechanism of 13-cis retinoic acid and the secretion of a single glycoprotein in mouse skin tumors is being evaluated to determine the relationship of the glycoprotein induction to mucous metaplasia and tumor regression. Results from such research will be useful in designing synthetic retinoids that enhance chemopreventive activity.

Studies of cancer patients have shown that those patients with low levels of vitamin A have more recurrence of disease. Patients with Stage I and Stage II melanoma are under study in order to determine if adjuvant therapy with vitamin A can prevent recurrence of their cancer.

The various aspects of vitamin D metabolism being studied include vitamin D requirements of term and premature infants, especially in terms of the clinical problems of neonatal hypocalcemia, infantile rickets and osteopenia. Studies suggest that late neonatal hypocalcemia, manifested by low total serum calcium, low parathyroid hormone and magnesium levels, and elevated phosphorous levels could be due to a defect in parathyroid hormone secretion perhaps related to a defect in magnesium metabolism. Vitamin D's role in the mechanism of this condition needs further investigation.

Since vitamin D is known to affect the rate of bone collagen maturation, one investigator has developed models of hypo and hypervitaminosis D in the suckling rat, and a new technology for determining the distribution and amounts of reducible and stable bone collagen cross links. The formation of covalent cross links in collagen contribute to the tensile strength of the collagen. In bone the intermolecular cross links predominate over the intramolecular cross links. Research has shown that with age, covalent cross links are reduced in vivo to the more stable cross links; results of this research as well as a clearer understanding of the role of the calcium, phosphorous and calciferol metabolites on bone mineralization are important to understanding the nature of the defects of mineralization in rickets and osteomalacia.

Two distinct mechanisms have been identified whereby intestinal calcium transport responds to the active form of vitamin D; one is by an initial response by existent villus cells and the second is a crypt cell response whereby calcium transport begins as the cells move into position on the villus membrane. Studies of osteopenia in chronic cholestasis have shown that serum 25-(OH) vitamin D₃ levels correlate with intestinal calcium absorption, although these parameters were not predictive of the histology of metabolic bone disease.

It appears from studies in rats that the majority of vitamin D₃ and 25-(OH) vitamin D₃ is transported from the jejunal sacs in the portal blood rather than the lymph, and that the absorption of 25-(OH) vitamin D₃ is greater than vitamin D. 1,25-(OH)₂ vitamin D₃ is transported also mainly in portal blood and is not dependent on chylomicron production. Although bile salts increase the amount of 1,25-(OH)₂ vitamin D₃ in the lymph, total absorption is only slightly increased. One investigator has shown that the pituitary gland, *vis a vis* growth hormone, is necessary for maintaining elevated 1,25-(OH)₂ vitamin D₃ plasma levels during phosphate

deprivation. In studies with chicks, the pure form of the 1,25-(OH)₂ vitamin D₃ receptor from intestinal mucosa has been isolated and four new vitamin D metabolites have been identified.

Patients undergoing hemodialysis appear to have a substantial reduction of photoactivation of vitamin D, despite the presence of normal concentrations of the substrate of 7-dehydrocholesterol in the epidermis. This finding represents an exciting new lead into the process of vitamin D activation in the epidermis. Establishing the appropriate dosage of the activated forms of vitamin D to treat more effectively children with diseases that lead to hypocalcemic disorders is an important research area.

High performance liquid chromatographic techniques have been used to assay vitamin D₂, vitamin D₃, 25-(OH) vitamin D₂, and 25-(OH) vitamin D₃ using very small samples in human milk. Preliminary results indicate that 25-(OH) vitamin D₂ and 25-(OH) vitamin D₃ occur in breast milk at concentrations of less than 0.5 mg/ml. Studies are investigating the use of enzymatic hydrolysis in order to release vitamins D₂ and D₃ from the breast milk lipids and the development of microassays for 1,25-(OH)₂ vitamin D and 24,25-(OH)₂ vitamin D. Additional research is under way to determine the role of vitamin D and its metabolite 1,25-(OH)₂ vitamin D₃ on lactation and its interaction with parathyroid hormone, calcitonin, and prolactin. Lactation represents a unique physiological condition for the study of the interaction of calcium-regulating hormones.

Vitamin E research deals with basic studies on its reduction potential, as well as the development of new assays and analogues of vitamin E. In studies on the use of vitamin E in the various hemolytic anemias, it appears to ameliorate the oxidative ravages of insufficient amounts of reduced glutathione in the anemias of glucose-6-phosphate dehydrogenase deficiency and glutathione synthase deficiency. Clinical investigations continue on the vitamin E requirements of premature infants by evaluating such factors as the presence of malaise, poor feeding, failure to thrive, infections, necrotizing enterocolitis, and bleeding problems in infants with low levels of vitamin E. The protective role of vitamin E in retrolental fibroplasia in premature infants is also being investigated.

Preliminary studies of the mechanism of action of vitamin E on platelet aggregation, release and adhesive properties suggest a direct influence of the vitamin on the fluidity of platelet membranes. It is hypothesized that vitamin E makes arachidonic acid in the membrane unavailable for oxidative conversions by cyclooxygenase and lipoxygenase. Vitamin E appears to be an effective in vitro inhibitor of platelet aggregation and release, and one of the few physiological antiaggregates. The in vivo effect of vitamin E supplementation alone and in conjunction with aspirin on platelet function will be evaluated in normal volunteers.

Investigators have shown that vitamin E in selenium deficient rats protects against lipid peroxidation in rats treated with 50 mg of methyl ethyl ketone peroxide per kg body fat, as measured by pentane production. Chronic ethanol consumption for 9 weeks did not influence lipid peroxidation in vitamin E and selenium deficient rats, even though the vitamin

E deficient rats produced twice as much pentane as rats fed vitamin E. Another study of vitamin E and selenium deficient rats has shown that adriamycin clearly stimulates lipid peroxidation in these animals. The degeneration of heart muscle often seen as a side effect of adriamycin use may therefore be caused by the peroxidative damage preventable by higher levels of vitamin E and selenium.

Research on vitamin K investigates the mechanism of vitamin K on protein carboxylation and the mechanism by which calcium is required in the formation of protein phospholipid with vitamin K dependent plasma proteins.

Research on the water soluble vitamins emphasize the mechanisms and metabolism of vitamin C, niacin, thiamin, folic acid, B₆, and B₁₂. Vitamin C as an antioxidant to inhibit intracellular oxidations and the accumulation of possibly toxic oxidized products is being investigated in terms of the prevention of retinal degeneration and formation of lens opacities or cataracts.

Folate is one B vitamin that received a great deal of research attention. Studies on the biochemical-genetic regulation of essential folate pathways in cultural human cells have detected 9 of the 15 major folate pathway enzymes in crude extracts of cultured skin fibroblasts, peripheral blood lymphoblasts, and in amniotic fluid cells. Skin fibroblasts from patients with inborn errors of folate metabolism are being studied in order to understand the biochemical changes in methylene tetrahydrofolate deficiency and dihydrofolate reductase deficiency. Investigators have found that in the presence of normal methionine synthetase activity, the rate of synthesis of methionine from homocystine is a function of 5,10-methylene tetrahydrofolate reductase activity, and that the measurement of the methionine biosynthesis capacity of cells deficient in this enzyme accurately reflects the clinical status of the patient from which the cells were derived. The enzymes, dimethylglycine dehydrogenase and sarcosine dehydrogenase, appear to be the folate binding proteins of the mitochondria, while a high molecular weight folate binding protein containing bound tetrahydropterol pentaglutamate has been purified from the rat liver cytosol.

Dietary folates that exist primarily as pteroylpolyglutamates are absorbed in the jejunum by hydrolysis and subsequent intestinal transport of pteroylmonoglutamyl folate. The intestinal mucosa enzyme, folate conjugase is required for this transformation.

The requirement for folate in pregnancy is an important research focus since a marginal deficiency of the vitamin may have an adverse effect on folic acid status and growth of the newborn. An animal model of marginal folate deficiency in the cebus monkey will be used to compare the sequential appearance of any clinical or biochemical signs of folic acid deficiency in the mother and the neonate to compare the folic acid status of the mother with the infant, and to ultimately estimate the folic acid requirements for pregnancy and lactation in the cebus monkey.

An important factor that enhances folate uptake by intestinal cells has been discovered in human milk, while a receptor protein that binds the

folate has been isolated from intestinal cell extracts. These findings imply that protein-mediated folate absorption occurs in infants. In addition, studies have shown that the uptake of radioactive free folate is greatly enhanced by the saturation of breast milk with nonradioactive folate, suggesting a complicated binding and uptake mechanism for folate.

Research suggests that approximately 10 percent of congenital malformations in phenytoin-treated epileptics may be induced by a decrease in the availability of folate. This effect has been shown to be species specific in that oral administration of phenytoin caused reduced levels of plasma folate in man and mice, but not in rats or guinea pigs. Altered folate metabolism is also implicated in the pathogenesis of Martin-Bell-Fragile X syndrome; an X linked recessive pattern manifested as mental retardation.

Studies of folate depletion in normal and SV40-transformed human fibroblasts have shown that after 72 hours the transformed cells contained 3 to 10 times more polyglutamate than the normal cells, although the growth rates for the normal and transformed cells are similar. Inhibition of polyglutamate formation therefore may be an important potential target for chemotherapy. A folic acid antagonist "x-methyl folic" acid that contains four more carbons than folic acid has been identified and could possibly be used as an antitumor agent in methotrexate resistant cancer patients.

Studies in rats attempt to determine the levels of S-adenosyl methionine and S-adenosyl homocysteine in the brains of rats fed diets lacking in B₁₂ (cobalamin), folate, and methionine. Levels do not appear to be affected unless the animals are treated with broad spectrum antibiotics when methotrexate is given to induce methyl deficiencies; none of the macromolecular methyltransferase enzymes or reaction products are affected.

Cobalamin deficiency, induced in the fruit bat model, appears similar to human pernicious anemia characterized by neuropathy but without hematologic complications. This model seeks to elucidate the metabolic role of cobalamin in nervous and other tissues and its interactions with folate. Cobalamin appears to enhance immunoglobulin production and release through IgG, as well as protein synthesis in normal and deficient human lymphocytes. This effect was enhanced by cobalamin per unit cell.

Niacin is present in foods chiefly as pyridine nucleotides. Metabolic studies have shown that nicotinamide is absorbed very rapidly by passive diffusion, while nicotinic acid is transported more slowly by facilitated diffusion with a greater proportion retained in the intestine and converted to nicotinamide adenine dinucleotide (NAD). Prior to absorption, NAD is largely converted to niacinamide through the actions of pyrophosphatase, phosphatase and glycohydrolase.

Studies are under way on thiamine's role in the function of the central nervous system. One research effort is concerned with the role of thiamine in neurotransmission and the mechanism of the demonstrated central nervous system dysfunction in early stages of thiamine deficiency. The neurodegenerative condition known as Leigh's disease appears to be

characterized by a disordered metabolism of thiamine-phosphate-esters in the brain. Investigators are attempting to purify cerebral thiamine-diphosphatase (TDP) and are measuring the cerebral synthesis of thiamine-triphosphate (TTP). TTP synthesis is blocked by an unknown factor found in urine of patients with Leigh's disease. In addition, studies are also investigating the interaction of thiamine pyrophosphate and branched chain ketoacid-dehydrogenase (BCKD). Thiamine appears to function at the site of enzymatic activity and produces a conformational change in BCKD that renders the complex more stable.

Biotin-responsive multiple carboxylase deficiency, a genetic disorder, can be prevented in utero by the administration of 10 mg. biotin per day to the mother during the last trimester of pregnancy. Thus, prenatal metabolic therapy of this enzymatic defect was successful by the oral administration of biotin to the mother during pregnancy which led to increased levels of biotin in cord blood and prevented the onset of profound biochemical and clinical abnormalities in the child.

A study on the special nutritional needs, including the need for vitamins, of the elderly is examining the nutritional status of 270 healthy individuals 60 years of age and older in an attempt to determine if illness is a consequence of subclinical malnutrition in healthy people and if nutritional deficiencies correlate with the decreasing ability to resist disease with age. Data gathered thus far show that the diets are generally adequate, except for the calcium and vitamin D intake of the women. Fifty-four percent of the women consume less than the RDA for vitamin D and their blood levels are low. In terms of vitamin C status, less than 2 percent of the individuals appear to be in danger of developing clinical deficiencies. The men, however, appear to need twice as much of the vitamin as the women in order to maintain optimal blood levels. Megavitamins have been shown to have little effect on immunological functions.

Behavioral Studies in Nutrition

The motivating forces controlling food selection and food intake are diverse. The physiological factors of taste, smell, gastric and humoral responses to certain foods are often influenced by social, cultural and religious values, as well as by learned habitual behaviors. Studies attempt to define the exact role of these values and behaviors on influencing food preferences and aversions, as well as define the influence of dietary intake on subsequent behavior. In FY 1982, NHLBI, NIADK, DRR, NICHD, NINCDS, NCI, and NIA supported studies in this area.

Studies on the neurophysiology of learned ingestive behaviors examine the neuroanatomical and neurophysiological integrations at the level of the neuron and synapse. For example, a "wiring diagram" describing the connection of motor neurons that explains swallowing behavior has been developed. The relationship of changes in feeding behaviors to fundamental structures and functions of neurons is being further defined in animals.

Another study examines the effect of angiotensin and other chemicals injected into various parts of the brain on drinking and feeding behaviors.

The receptor site within the brain for the dipsogenic action of angiotensin is being sought, with particular attention paid to the subfornical organ. Antidipsogens (prostaglandin E and substance P) are also under investigation for their selective competitive interaction with the dipsogenic action of angiotensin. The hypothesis that sodium appetite is aroused by a synergistic effect of angiotensin and aldosterone is another area of research interest.

In order to examine the chemical controls of food intake, physiological doses of catecholamines are being examined for their role in adrenergic mechanisms that either arouse or suppress the brain mechanism for feeding behavior.

Studies on the neuroanatomical connections from the viscera (especially esophagus and gut) to the brain attempt to describe the electrophysiological circuit activity from the central gray matter to the lateral parts of the brain that affect food intake. Many of these circuits appear to be of a reciprocal inhibitory nature, while connections to the limbic brain areas may be important for the emotional activity associated with eating. Studies of the hypothalamus and other parts of the midbrain indicate that neuroendocrine cells, in particular, change their activity with changes in the chemical and electrical surroundings. Chemical changes, especially of glucose and salt concentrations in the circulating blood, appear to affect the electrophysiological activity in certain areas of the brain; specific concentrations are associated with increased food intake, while others are associated with a decrease.

Studies carried out at the Regional Primate Research Center investigate the role of peptide hormones in the control of food intake and body weight in the baboon (Papio cynocephalus). Small amounts of insulin infusion into the cerebrospinal fluid appears to have a negative feedback control to the brain for food intake. The decrease of food intake and body weight is dose dependent. Studies to define the mechanisms for regulating eating behaviors and energy expenditure are also under way in rhesus monkeys (Macaca mulatta).

The ontogeny of drinking and feeding behavior is also being studied in suckling and weaning rats in order to describe the chronology of the physiological controls for each behavior as the animal matures. Studies of the glucostatic mechanisms for controlling suckling and nibbling latencies of rat pups have shown that suckling does not come under glucostatic control until the time of weaning at approximately 24 days, while nibbling behaviors come under glucostatic control at 21 days. These findings indicate that by day 21, rat pups have developed a specific appetite for carbohydrate and when challenged with a glucoprivic agent, their feeding behavior is directed towards a food source high in carbohydrate.

Another investigation in rats on the physiological basis of weaning indicates that elimination of the surges of thyroxine and corticosterone hormones that appear just before weaning delays its onset. However, early treatment with either thyroxine or corticosterone do not appear to cause early weaning. Neither hormone therefore is the trigger for weaning but rather plays a permissive role.

Investigators have found that emetic areas of the brain stem mediate the acquisition and extension of conditioned taste aversions. It appears that olfaction is involved in both food selection and peripheral defense. Odor-taste interactions during flavor conditioning are being studied in terms of illness induced food aversions. Odors, when presented in conjunction with taste, become strongly associated with a food if ingestion of the food is followed by an illness. This phenomenon of potentiation is being studied and is known to be related specifically to feeding behavior. Potentiating odor-taste interactions do not occur if shock reinforcement is used. It appears that taste cues can index odor cues in memory as food-related stimuli. Lesions of the taste cortical area of the brain produce very specific disruptions in taste aversion conditioning, but do not affect odor illness conditioning or conditioning of taste potentiated odor aversions. The vagus nerve also plays different roles in flavor conditioning with vagotomized rats failing to acquire normal aversions--either taste, odor or potentiated odor--when the illness induced agent is a gastric irritant. Thus, severing the vagus nerve seems to eliminate an important component of the conditioned emetic response.

The Communicative Disorders Program supports basic studies of the neurological mechanisms of taste in a variety of animal models i e , rat, hamster, sheep, gerbil and dog. X-ray crystallography is used to study the biomedical models of sweet taste. This program also supports human clinical studies through the Chemosensory Clinical Research Centers on the relationship of taste to diseases such as diabetes, obesity, renal disease, and radiation-induced illnesses.

A number of studies investigate the role of specific nutrients or nutritional status on behaviors. Of special significance are the studies on nutrition, neurotransmitters, and behavior in terms of the effect of specific dietary nutrients on the levels of neurotransmitter precursors in the brain and in turn the amount of neurotransmitters formed. Tryptophan is converted into serotonin; tyrosine is converted into dopamine, norepinephrine and epinephrine; and choline is converted into acetylcholine. These end products are all neurotransmitters. Research has shown that an increase in the brain level of the precursor enhances the synthesis of the corresponding neurotransmitter, which in turn increases the transmission of signals from the neuron to the cell it innervates. Tyrosine and choline, however, amplify neurotransmission selectively, increasing it at some synapses but not at others.

It is known that the proportion of protein and carbohydrate in the diet influences the conversion of tryptophan to serotonin, the neurotransmitter which delivers signals to scattered groups of neurons that control sleep, mood and appetite. Data indicate that feeding animals large amounts of protein causes a reduction of brain levels of tryptophan and the synthesis of serotonin. This reduction is mediated by the ratio of plasma tryptophan to five other amino acids in plasma (tyrosine, phenylalanine, leucine, isoleucine, and valine), which compete for a carrier molecule needed to transport them across the blood-brain barrier. Because most proteins contain less tryptophan than the other five amino acids, a high protein meal reduces the ratio of tryptophan to the competing amino acids in the

plasma. A high carbohydrate meal, on the other hand, has the opposite effect, as the insulin which is secreted reduces the plasma levels of the other amino acids more than the level of tryptophan. The serotonin-releasing neurons in the brain serve as sensors of the ratio of tryptophan to the other amino acids in the plasma; serotonin release increases after a carbohydrate meal and is reduced after a high protein meal. Thus, eating a meal rich in carbohydrate and poor in protein generates a neurochemical change--namely increased serotonin synthesis that causes the animal to reduce its intake of carbohydrate but not of protein.

Most people appear to need 6-12 grams of carbohydrate to elicit the secretion of sufficient insulin to lower plasma levels of the large neutral amino acids (LNAA), while 25 grams are needed to raise the plasma tryptophan/LNAA ratio and thus enhance brain serotonin synthesis. Obese people may suffer from a disturbance of this remarkable feedback mechanism that links nutritional, metabolic, and neurochemical and behavioral systems.

The clinical application of research on nutrient-neurotransmitter relationships has been particularly relevant to treating patients with tardive dyskinesia (the impaired ability of voluntary movement seen in the elderly, induced by long-term use of certain drugs such as tranquilizers), high blood pressure, depression, Parkinson's disease, and other disorders. In patients with tardive dyskinesia, choline and lecithin have been shown to effectively prevent the side effects seen with the prolonged administration of antipsychotic drugs. The neurons that suppress the symptoms of the disease are apparently sensitive to the additional supply of choline. Lecithin therapy may also prove useful in treating memory disorders associated with old age.

Tyrosine in its role as precursor of norepinephrine may be an effective antihypertensive agent. The possible therapeutic value of tyrosine for depression is also under investigation. Many psychiatrists believe that depression reflects the inadequate neurotransmission mediated by norepinephrine and possibly serotonin. Other studies have shown that the administration of 100 mg/kg/day of tyrosine to patients with Parkinson's disease enhances catecholamine release from frequently firing catecholaminergic neurons. Studies in rats have shown that 100 or 150 mg/kg of tyrosine in a single oral dose significantly increases urinary levels of all catecholamines and their metabolites for approximately 2 hours. Thus, in humans as well as in rats, tyrosine may enhance catecholamine release from both central and peripheral tissues.

Another study in rats has shown that relatively small variations in the protein/carbohydrate ratio of a diet given for short periods of time significantly altered the motor activity of rats; an increase in the ratio made the rats more continuously active. Thus changes in the diet can significantly alter behavior.

A number of investigations are under way to examine the behavioral effects of protein calorie malnutrition, iron deficiency, zinc deficiency, and heavy metal toxicity. Studies on the development of the central nervous system and the resultant behavior in rats fed protein deficient diets (8 percent versus 25 percent in controls) reveal a marked increase in the

regional concentrations of cerebral norepinephrine, altered hippocampal electrical activity with increased theta activity, hyperactivity to aversive stimuli such as electric shock and increased copulatory activity. In addition, low protein diets fed prior to conception produce substantial changes in the physiological properties of spontaneously active cells in the frontal neocortex. The same protein malnutrition effect was also apparent with a low protein diet given immediately at birth following a normal gestation. Thus, the period of vulnerability to developmental malnutrition extends into the lactational period. It is important also to note that a normal diet given to rats after gestation does not reverse the effects of gestational protein malnutrition.

Other scientists attempt to separate the effect of malnutrition and environmental variables on behaviors. Malnourished rat pups, mother deprived and reared by nonlactating aunts, were found to be slower than controls to habituate to open field testing. Environmental effects, such as handling were found to produce behavioral effects as strong as those of undernutrition. This study also noted that malnourished rats benefit less from environmental enrichment than normal animals.

Studies on the effect of zinc deficiency on exploratory behaviors in young monkeys include tests of climbing, exploration manual dexterity, oddity learning, social motivation and behavior, level of arousal, and organization of behavior. Results indicate that offspring of zinc deprived mothers had less exploratory behavior activities in the absence of any overall alteration in locomotor activity or arousal levels. Zinc deprived offspring did not appear to be deficient in learning spatial delayed responses and brightness discrimination tasks, although the error patterns in these animals were similar to the type common in monkeys with brain damage due to prenatal anoxia or developmental exposure to toxins.

Another study on the behavioral effects of lead exposure from dietary, maternal, and airborne sources are being assessed through neuropsychological performance tests of infants and school children with high and low levels of cord-blood and dentine lead, respectively. Initial results indicate that children's behavioral outcome measures were dose related to lead, with the poorest performance associated with the highest levels of dentine lead. Elevated dentine lead levels increase a child's risk of needing daily remedial academic aid; 50 percent of the children above the 90th percentile of lead distribution received remedial aid versus 16.9 percent of the children below the 90th percentile. The children's IQ scores (WISC-R) appeared to fall short of expected IQ scores with elevated levels of dentine lead (20 parts per million)

Nutrition, behavior, and changes with age is another area of investigation. Research has shown that moderate to severe undernutrition after weaning extends a rat's lifespan by as much as 50 to 100 percent. A study is under way to study sensory motor and cognitive function (learning and memory) in such rats whose lifespan has been prolonged by undernutrition. In addition, changes in learning, and memory storage and retrieval are being analyzed in the normal rat with age. Individual differences between the normal rat and an undernourished rat with age will be compared in terms of the rate of loss of both sensory motor and cognitive function.

A study on gustatory and olfactory quality changes with age has shown that older subjects have a lower taste and smell acuity. Thresholds for taste are increased by a factor of 2.5 for amino acids and 2.7 for sweeteners. This decreased acuity for sweeteners can lead to weight gain with addition of nutritive sweeteners, and adverse dose-related biological effects with artificial sweeteners. The decrease in olfactory acuity is greater than that for taste, with olfactory thresholds for a series of artificial food flavors shown to be 11 times greater in the elderly than in the young. The data show that in addition to the age-related losses in thresholds, perception of the growth in intensity with concentration and discrimination is also reduced. The ability to discriminate among odors is also greatly reduced.

Sensory losses do not appear to be uniform across stimuli; for example, the odor of 2 methoxy 3 isobutyl pyrazine (green pepper) was discriminated from the alkyl pyrazines, but alkyl pyrazines were not discriminated from each other. Also, of the L amino acids, more age-related taste loss appeared for L-glutamic acid and L-aspartic acid.

Social factors and health changes with age also affect dietary habits. Patterns of carbohydrate consumption of adults aged 65 to 74 years have been analyzed in terms of living arrangements, i.e., living alone, living with a spouse only, living with a spouse and children, living with a non-relative, living with a parent or other relative, and single head of a household. Carbohydrate intake as a proportion of total calories, number of carbohydrate servings per day or proportion from complex carbohydrates were consistent across living arrangements, except for single heads of households and nonmarried persons living with a relative where complex carbohydrate use seemed lower. However, calories from complex carbohydrates were greater for the older adults than for younger adults, regardless of living arrangements. Thus, the elderly appear to rely on fruits, vegetables, breads and cereals as carbohydrate sources. Another study will examine how dietary intake and habits are affected when adults 62 years of age and older are moved from age-dispersed to age-segregated housing. The study will identify those persons whose eating is most responsive to external stimuli in order to identify those individuals most at risk for nutritional deficiencies when environmental changes occur. Social networks, and factors determining experienced stress and effectiveness of coping in older persons will be examined in relation to eating patterns.

Another epidemiological study that examines the effect of socialization and modernization on a specific population's nutritional status is studying Samoans who move to California. This study indicates that they undergo a more significant increase in weight and cardiovascular risk than those Samoans who move to Hawaii. This appears to be due to an increased level of industrialization, rather than purely genetic risk factors. To further explore the effect of modernization on several measures of cardiovascular aging, research in a Tibetan population will examine the influence of attitude, activity, the timing of events in the life cycle, and other environmental variables on biological aging in infants, adolescents, and adults.

The effects of cultural, social and economic factors on trends in breast feeding are being investigated in the Pima Indians, the Negev Bedouins and middle class black and white mothers in the U.S. A pilot study conducted in the District of Columbia revealed the incidence of breast feeding in an urban hospital at 75 percent. Of those women who breast fed their infants, 70 percent were white, 86 percent were married, highly educated (15.8 mean years), and older (mean age 29). Of the women choosing to bottle feed, 80 percent were black, 50 percent were unmarried, the average age was 25 years and the average number of years of schooling was 13.5. The increase in breast feeding in the U.S. has been most pronounced among white women, primarily of the higher socioeconomic groups. The duration of breast feeding also seems to be on the upswing, especially among the upper socioeconomic status white women. This pilot study also revealed the following factors as influencing the women's rationale for weaning before 4 months: insufficient milk, baby rejected the breast, and mother's return to work. In addition, 57 percent of the short-term breast feeders used formula in the first month postpartum with the claim of insufficient milk as the primary reason for introducing the formula.

Studies have reported a strong "within culture" correlation between food attitudes of parents and their children, especially in the area of disgust and contamination sensitivity. It seems that the child's conception of food develops in the following sequence: children less than 2.5 years reject only foods that are distasteful; later, they reject foods because of anticipated harm or danger; and rejections due to disgust appear last. The rejection of good foods due to contact with offensive substances--a hallmark of disgust--does not appear until 6 years of age. The youngest children believe that something that is bad for them will taste bad.

Data on the child malnutrition rates in Papua, New Guinea have shown that these rates follow cultural rather than environmental boundaries. The highest reported rates in the Sudest Island area of New Guinea correspond with the area where traditional proscriptions against feeding young children animal protein foods are scrupulously followed. These proscriptions may be a cultural adaptation to the local environment of hyperendemic malaria, a major cause of child mortality.

Various social, familial, and personality factors that influence persons who develop anorexia nervosa are being examined. Data indicate that anorectics have a phobia of ingesting food and gaining weight, maintain an avid interest or even an obsession with food and flavors, and do not report a loss of appetite or hunger. A study is under way to examine the role of standards of physical attractiveness and ideal body physique in anorectics and normal weight adolescent subjects with no history of being significantly underweight or overweight. Significant sex differences have been seen in the perceptions of normal weight. The normal weight females exhibited a desire to be thinner even though their present body weight appeared normal, and they expressed a significant preoccupation with food and dieting. The males, however, reported their ideal weight as consistent with their present weight or even higher. The females' idea of physical attractiveness followed a norm of extreme slenderness.

Many studies investigate various methods to change health behaviors, particularly in terms of diets associated with different diseases. The Stanford Heart Disease Prevention Program continues its communitywide programs for primary prevention of cardiovascular disease through development and distribution of new brochures on blood pressure control, brief television spots on weight control and a multimedia smoking cessation program. Changes in the risk factors for cardiovascular disease, including dietary habits, are being assessed in 1,400 subjects of the control and intervention communities. The Minnesota Heart Health Program and the Pawtucket Heart Health Program are other community based demonstration studies investigating the influence of community intervention efforts on changes in health behaviors associated with cardiovascular risk.

Additional types of demonstration projects are designed to modify a family's risk for cardiovascular disease to explore the possibility that dietary change and/or relaxation training will reduce the need for medication in hypertensive individuals; to determine the medical cost-effectiveness of specific interventions designed to improve blood pressure control in defined populations; and to assess the effect of educational behavioral programs directed at high risk patients and families.

Changes in eating behaviors, particularly anorexia nervosa and taste aversions, are common problems in cancer patients. One hypothesis being tested is that anorexia, associated with neoplastic disease, is secondary to peripheral metabolic changes induced by the presence of a tumor.

Research has shown that in neoplastic disease the increase in nonesterified fatty acids displace tryptophan from albumin making it more available for entry across the blood-brain barrier. Therefore, by manipulating the plasma concentrations of free or total tryptophan, or other competing large neutral amino acids, or by administering serotonin antagonists, physicians may prevent the development of anorexia. Another study seeks to determine whether taste aversion problems found in clinical radiation and gastrointestinal chemotherapy result from induced taste aversion. The effectiveness of progressive muscle relaxation (PMR) in reducing psychological anxiety, nausea, and vomiting in two groups of cancer patients is also being examined in terms of the effect on nutritional status.

Studies on nutrition and behavior in relation to treatment for obesity examine various behavioral changes necessary for weight reduction. In a home based behavioral program for obese children, parents are being trained to model appropriate eating or exercise behaviors for their overweight child to imitate. Results of the study indicate a much greater success rate for children at maintaining normal weight if their parents were actively involved in the weight reduction program. This study will also examine the relative importance of eating control versus exercise in the management of childhood obesity.

Training children to eat slowly and pause more frequently between bites is also being examined as an effective method to achieve long-term behavioral changes related to preventing the onset of obesity. Also, teaching preschool children positive health and dietary behaviors has been shown to initiate such behaviors, especially if the information and materials being used are fun, age-relevant, and usable by the child.

The effect of dietary intervention on behavioral changes in children with the various inborn errors of metabolism is also being investigated. For example, studies have shown significant increases in the mean full scale IQ scores of children with phenylketonuria (PKU) who remain on a low phenylalanine diet after the age of 6. Achievement tests for spelling and reading also revealed small but significant differences in favor of those who remained on the diet at 8 years of age.

Results of rat studies on the cause of brain damage in phenylketonuria have shown that elevated levels of phenylacetate in the rapidly growing brain induce biochemical, structural, and behavioral deficits that simulate experimental hyperphenylalaninemia. The deficit in cognitive function seen with this metabolic error may be related to deficient synaptic development or to interference with acetyl CoA synthesis or utilization. Another animal model of hyperphenylalaninemic rats also has shown impaired latent learning and observational learning.

A study of seven girls, symptomatic heterozygotes for ornithine transcarbamylase deficiency, involved dietary treatment combining protein restriction (1-1.5 g/kg/day) with arginine supplements (1 mmol/kg), benzoate (250 mg/kg) and/or phenylacetate. As a result of the treatment, one girl showed a decrease in plasma ammonium levels toward normal, improvement in hyperactivity and irritability behaviors, and an increase in her IQ score. A relationship appeared to exist between the magnitude of hyperammonemia, the duration of coma, and neurodevelopmental progress.

A high incidence of migraine headaches and protein intolerance manifested by cyclical vomiting, particularly among heterozygote women, has been detected in families with evidence of ornithine transcarbamylase deficiency. Other studies of urea cycle enzyme defects have shown that heterozygotes, although having full scale IQ scores within the normal range, did appear to have significantly larger verbal-performance IQ differences--an indicator of cortical dysfunction. Perceptual and motor function changes were studied in heterozygotes following an alanine challenge in order to evaluate the effect of asymptomatic hyperammonemia on cortical dysfunction. No acute changes were noted with modest hyperammonemia.

A pilot study of voluntary protein intake of asymptomatic heterozygotes for urea cycle enzyme deficiencies suggest that these individuals may, in fact, unknowingly restrict their protein intake. The protein intake for 3 days for the heterozygote women averaged 0.6 ± 0.1 g/kg/day while that of their unaffected spouse average 1.2 ± 0.3 g/kg/day.

Elevated plasma ammonium levels during the first 2 months of life have also been found in more than 50 percent of the low-birth-weight infants. Arginine supplementation (1-2 mmol/kg/day) beginning in the first 2 weeks of life was found to be effective in lowering plasma ammonium levels to normal.

Studies of the possible long-term effects of this clinically asymptomatic hyperammonemia on neurological integrity of the infant include measures of auditory habituation and primitive reflex profiles. Interim results from the Bailey Infant Development Scales indicate no significant differences

in auditory habituation, primitive reflex profiles or IQ between infants having normal ammonium levels, hyperammonemia-arginine treatments, and hyperammonemia without treatment.

Child and Infant Nutrition

Genetics and the effect of environmental influences, such as nutrition, play a major role in the proper growth and development of infants and children. In FY 1982, NICHD, NHLBI, DRR, NIADDK, NIAID, NCI, NIDR, NINCDS, NIEHS, and NIGMS supported research in child and infant nutrition.

In order to clearly understand growth and development throughout the life cycle and under certain conditions research continues to better define the nutrient requirements of normal term infants at birth and during the first year of life, and the requirements of the low-birth-weight premature infant and growth retarded infant. The requirements for protein and energy, vitamins, minerals and trace elements for maintaining acceptable rates of extrauterine growth and development must be ascertained.

In terms of establishing the nitrogen requirement of infants, some metabolic studies have raised serious questions about the validity of the nitrogen balance technique. Other studies continue to investigate the influence of zinc on fetal and neonatal development in normal infants and those with failure to thrive, as well as the bioavailability of zinc added to breast milk versus bovine milk. Low zinc content in breast milk was shown to result in acrodermatitis and hypozincemia in 9-week-old premature breast fed infants; these symptoms were alleviated within seven days with oral zinc supplementation. Zinc secretion into breast milk appears to be a controlled process independent of zinc intake and serum levels. Additional studies have shown that a low zinc intake decreases appetite and can limit skeletal growth rates of rapidly growing young children.

Data from animal studies indicate that rat pups from mothers made zinc deficient during the last week of gestation and the following 18 days of lactation develop more dental caries than controls. In other studies on the development of teeth and caries resistance, the role of fluoride as well as the role of vitamin A in the calcification of teeth and bones is being investigated.

Additional attempts to determine specific nutritional demands and to uncover the possible role of nutrition before and immediately after birth has led to exploring the environment of the fetus and neonate. For example, studies to devise the appropriate nutrient therapy for the low-birth-weight infant involve controlling the complex functions of the placenta for as long as several months. Investigations are under way on total parenteral and enteral nutrition, metabolic balance and calorimetry, and research on immunological and nutrient composition of colostrum and human milk from mothers who deliver at various gestational ages.

Research has shown different rates of growth in the low-birth-weight infants by adjusting the caloric and nutrient density of the diet. A 3-year, carefully controlled clinical study, initiated in FY 1982, is

designed to compare growth and development of low-birth-weight infants fed isocaloric and isonitrogenous preparations of human milk and formula. Physical growth, immunological development, and gastrointestinal function of these high risk infants will be evaluated in response to the biologically active components believed to be present in breast milk.

The appropriate nutritional therapy for the premature infant must take into account the immaturity of various enzyme and transport systems, since these systems become saturated at nutrient concentrations that vary directly with gestational age. A high rate of physical growth while keeping the circulating substrates and metabolites within acceptable ranges must be maintained. Investigators have found that premature infants lack the enzyme capability to manufacture tyrosine, arginine, cysteine and cystine, as well as taurine and histidine. These six amino acids, in addition to the eight required by adults are therefore essential to the premature infant. When the concentration of any of these essential amino acids falls below a certain critical level, it becomes rate-limiting in terms of growth. Methionine intake has been shown to be limited with certain infant formulas; therefore, studies are measuring 3 methylhistidine excretion of infants fed soy formula diets supplemented with methionine.

In addition, the premature infant has minimal stores of carnitine which is important for fatty acid transport across the mitochondrial membrane; hence, the enzyme activity responsible for its synthesis is probably low. Since all soy based infant formulas are devoid of carnitine, the nutritional management of these infants can become complex. Studies are also under way on the effect of medium chain tryglycerides and taurine on fat absorption in the low-birth-weight infant.

The proper protein intake for premature infants has yet to be resolved. Some investigators believe that intakes in the range of 2.5 to 3.0 g/kg/day (two to three times that supplied by human milk) are needed to maintain a growth rate comparable to a fetus of a similar age. Therefore, supplementary cow's milk protein would be needed. Other investigators still believe that the unique composition of human milk makes it ideally suited for the nourishment of these infants.

Studies on infant feeding have shown that infants during the first few days of life prefer sweeter formula feedings (i.e., sucrose over lactose and fructose over glucose). One study of normal female infants from 8 to 112 days of age found that infants fed the sucrose-containing formula had greater mean energy intake per unit of body weight and greater mean gains in weight than those infants fed polycose (a cornstarch hydrolysate of bland taste). Results from this study suggest that differences in the type of carbohydrate in an infant formula influence food consumption; however, with longer term feeding (>20 to 28 days), adaptation to the formula might occur in that the infant may adjust formula consumption to meet energy needs independent of the type of carbohydrate in the formula. The possibility that differences in sweetness may lead to differences in weight gain and/or body composition requires careful research assessment.

The development of the digestive function in the newborn is another important area of research. The newborn has a limited supply of energy

reserves in the form of body fat, and its intestinal tract must adapt very quickly to support all of the infant's energy and growth needs. A complex series of secretions released from the oral cavity, stomach, and intestine play a critical role in digestion and absorption of fats, complex carbohydrates, and protein. Several studies are under way to characterize the progression of digestive processes that are turned on near the time of birth and thereafter. In terms of fat absorption, an animal model has been developed to analyze bile acid secretion in the newborn, while another study investigates the role of fat ingesting enzymes secreted in the mouth and stomach. Research has shown that lingual lipase is a major contributor to fat digestion throughout postnatal development.

Studies are also under way to identify the numerous maternal factors that influence the mechanisms of fetal gastrointestinal development; these factors include the mother's nutritional status before and during pregnancy, maternal genetic makeup and hormonal status. Two systems have been developed to study the mechanisms controlling morphogenesis of the small intestine.

In order to explore the premise that hippocampal and cerebral development in the neonate and differentiation of hypothalamic mechanisms at this critical time could result in deficits in later reproductive function and in learning and activity, the effects of polychlorinated biphenyl (PCB) exposure during early postnatal development is being investigated in the rat. Lactating rats are exposed to three different doses of PCB immediately after the birth of their offspring in order to investigate the PCB's effect on reproductive ability, mating behavior, and activity learning in the female offspring when they reach adulthood. Other research on nutrition and neurological development is investigating whether early undernutrition causes abnormalities in the synthesis or structure of gangliosides and glycoproteins in the synaptic plasma membranes (SPM). Data have shown that the offspring of rats fed either a protein-calorie deficient diet or a protein-deficient diet during lactation had a significant deficit of SPMs as assessed by SPM protein content. This deficit was greater in the hippocampus and forebrain than in the cortex or cerebellum.

The composition of human milk and the special functions of its components is an important research area relevant to infant nutrition. Special analytical procedures are being used to determine the full range of lipids present in the milk throughout the lactation period, as a result of maternal age and diet. Trace elements, and amino acids and protein fractions of human milk and colostrum are also being evaluated. One project is evaluating the effect of medications used during labor and delivery, as well as smoking and prescription drugs on the composition of milk.

Immunological properties of human milk are believed to make a major contribution to effective host resistance during infancy. Studies are under way to evaluate the functional properties of the lymphocytes and macrophages found in colostrum and milk. Investigators have determined that human milk contains high concentrations of lactoferrin and lysozyme (two soluble proteins that inhibit bacterial growth in the gastrointestinal tract of human newborns; lactoferrin by binding the iron required for bacterial growth and lysozyme by bacterial lysis); secretory immunoglobins

(IgA) that coat the newborn infants' intestinal lining and are directed against bacterial antigens to which the mother and infant are exposed; macrophages, T lymphocytes and B lymphocytes that appear to play a role in neutralizing the effects of viruses, bacteria, bacterial toxins, and other foreign antigens including allergenic food antigens; and several growth factors (mitogens) that stimulate DNA synthesis and induce divisions in cells grown in culture. Breast milk mitogenic activity is concentration dependent, is greatest early in lactation, and may play an important role in the growth of intestinal mucosa cells.

In order to understand the immunologic responses to different products and regimens proposed for feeding infants when mother's milk is not available, a longitudinal study was carried out on the levels of specific antibodies in infants fed cow milk and soybean proteins. Data from the study reveal that the continuation of cow milk feeding beyond 112 days causes the mean values for the levels of antibodies to milk protein to increase, and perhaps reach a plateau by the age of 196 days (6-1/2 months).

This research indicates that the magnitude of the antibody response to milk protein is affected by the nature of the food protein, the concentration in the product, and the heat treatment applied during the processing. In addition, the type of initial feeding appears to influence the antibody response to milk products introduced later; i.e., the antibody response to pasteurized cow milk introduced after initial soy feeding was significantly greater than when introduced after cow milk feeding. This study reveals that soy products fed from birth to 4 months of age did not prevent a brisk antibody response to cow milk introduced later in infancy. Thus, from an immunological standpoint, when mother's milk is not obtainable the preferred substitute formula for infants appears to be a heat-treated lower protein, cow milk base product rather than a soy product.

The increased awareness of the nutritional value of breast milk has stimulated the establishment of a number of milk banks in the U.S. and throughout the world. Such milk banks serve to supply milk for clinical care and clinical investigations on infant nutrition, to bank milk for later feedings to normal infants, and to allow mothers to store milk for feeding her infant when she is unable to breast feed. A workshop, "Breastmilk Banking: Current Status and Future Needs," was held in FY 1982 in order to compile information on current milk banking techniques and to project future needs for banked milk as well as potential future methodologies.

Research on human milk banking continues to investigate techniques of collection, fractionation, storage and distribution of human milk as well as the effects of maternal factors on breast milk composition. Preserving the viable immunologically active cells in human milk and colostrum involves determining methods of high temperature, short duration heat processing that destroys the bacterial and viral contaminants while at the same time leave intact the biologically active properties of the milk, i.e., the immunoglobins, lysozymes, lactoferrin and growth factors. Maternal factors such as age, nutritional status, smoking, diet and duration of lactation are investigated in terms of their effect on breast milk composition and volume.

In an attempt to understand the production of milk in the mammary gland and the biological basis for lactation failure an animal model that isolates mammary end buds by microdissection has been developed and is now being used to evaluate the hormonal controls that govern the release of specific enzymes into the milk. Another system, an affinity chromatography system for isolating the estrogen receptors from mammary tissue, has also been developed and will be used to characterize the biological events of mammary development during the reproductive cycle.

Studies are under way on the physical and mental development of infants with various kinds of malnutrition including protein-calorie malnutrition, specific nutrient deficiencies and excesses (e.g., iron deficiency or lead excess), or malnutrition brought about by inborn errors of metabolism. Undernutrition often occurs in various disease conditions such as cancer, as well as with the inborn errors of metabolism such as phenylketonuria, galactosemia, homocystinuria, and other disorders of sulfur amino acid metabolism. Highlights of the research on the inborn errors of metabolism are described in detail as part of the special interest area on "Nutrition and Genetics."

Work on protein calorie malnutrition (PCM) in infants has revealed the existence of an intrinsic though reversible disorder of polymorphonuclear leukocyte motility with findings of diminished chemotaxis, increased cell adherence, activated cell morphology and unipolar distribution of surface adhesion sites with neutropenia. Such data suggest that the PCM child represents a new example of a leukocyte aggregation syndrome that may be caused by complement activation and sepsis.

A number of studies of pediatric patients carried out by the Clinical Nutrition Research Units involve the formulation and evaluation of various mixtures used for total parenteral nutrition (TPN). Examples of specific research include studies on the effect of cystine and taurine supplementation to TPN solutions in infants; the metabolic fate of intravenous fat emulsions; the effect of quantity and source of calories on nitrogen balance; net amino acid balance during TPN; hepatic dysfunction; the effect of amino acid infusions on plasma amino acid patterns; growth and metabolic variables of very low-birth-weight infants on combined enteral-parenteral feeding regimens; and the prospective evaluation of several modes of nutrition support (i.e., enteral, partial parenteral, peripheral nutrient infusion with enteral nutrition, and total parenteral nutrition) in children receiving multimodal treatment of stages II to IV Wilms' Tumors.

Additional research considers alterations in lipid metabolism in cystic fibrosis, irritable colon of childhood, optimal intakes of zinc and copper in pediatric patients, nutritional status assessment procedures, the use of 1,25 dihydroxyvitamin D₃ in steroid induced osteopenia, and the effect of chronic dialysis on vitamin and trace mineral hemostasis in children.

It appears that in children with moderate renal insufficiency, a restriction of dietary phosphorous increases the plasma concentrations of 1,25 dihydroxyvitamin D which reflects a reduction of and suppression of 25-hydroxyvitamin D-1 and hydroxylase activity. Additional studies in children show that oral phosphorous loading suppresses plasma levels of

1,25 dihydroxyvitamin D despite an increase in serum levels of parathyroid hormone. These findings together with animal data provide strong evidence that phosphorous intake plays an important role in the regulation of 1 α hydroxylase in the remaining functioning nephrons.

In studies of pediatric head trauma patients, the extent of hypermetabolism is being evaluated. Indices of hypermetabolism (oxygen consumption, nitrogen excretion, altered hormonal milieu) are being correlated with nutritional status, catecholamine levels, physiological reflections of increased sympathetic nervous system activity, and neurological outcome. It is hypothesized that a sustained elevation of catecholamines will be found after head trauma which mediates profound changes in metabolism and may impede neurologic recovery. Efforts are being undertaken to improve neurologic recovery after head injury by appropriate nutritional assessment and therapy.

Research on obesity in children examines the physiological effects of diet and exercise in obese children; behavioral precursors in infant obesity; early nutrition and the development of obesity; fat and fat-free body composition in children. In children with Chron's disease, usually manifested by growth retardation due to intestinal obstruction, abscess formation and decreased intestinal absorption, special diets administered to the children appears to increase their growth velocity.

Nutrition and Genetics

Research on genetics and nutrition include studies on inborn errors of metabolism; metabolic differences in nutrient requirements; chromosomal aberrations and determinations of cellular function, especially DNA repair mechanisms; and the effects of dietary intervention on inherited diseases or conditions. NHLBI, NICHD, NIADDK, NCI, DRR, NIEHS, NINCDS, NEI and NIA supported research in this area.

The study of genetic variants in man and in animal models helps to advance our understanding of both normal and abnormal biochemistry. The various inborn errors of metabolism under investigation include phenylketonuria, galactosemia, maple syrup urine disease, urea cycle enzyme deficiencies (isovaleric acidemia, hyperglycinemia, hyperargininemia, citrullinemia, methylmalonic aciduria, hyperornithemia, hyperlysinemia), biotin responsive carboxylase deficiency, cystinosis, and Menkes' kinky hair syndrome. Research continues on the dietary manipulations often used to overcome or bypass the enzymatic defects that characterize the inborn errors of metabolism.

Elimination diets have been shown to prevent the accumulation of nutrient substrates in metabolic pathways prior to the metabolic defect. For example, patients with hyperargininemia have shown a steady clinical improvement when treated with semisynthetic diets of N equivalent 0.6 gm/kg/day. In addition, preliminary findings from studies of gyrate atrophy of the choroid and retina suggest that controlling the blood level of ornithine through arginine deficient diets or pharmacologically through agents that increase excretion may modestly improve vision.

In an attempt to develop appropriate elimination diets for the treatment of familial hyperlysinemia, investigators have found that this inherited condition is caused by a deficiency in either one of the first two enzymes involved in the degradation of lysine. They have also initiated studies on the metabolism of pipecolic acid, an amino acid related to lysine and found to be elevated in patients with glutaricaciduria and pipecolic acidemia.

Other suggested treatments for various genetic disorders include using large quantities of vitamins to alter the decrease in cofactor affinity. For example, large quantities of pyridoxine are given to patients with pyridoxine-responsive seizure disorders or pyridoxine-responsive homocystinuria in order to overcome a decreased affinity of the apoenzymes (glutamate decarboxylase and cystathionine synthetase respectively) for their vitamin B₆ cofactor. Similarly, treating patients having multiple carboxylase deficiency (propionyl CoA carboxylase and 3 methylcrotonyl CoA carboxylase) with large amounts of biotin has resulted in complete clinical recovery.

Increased dietary intake of the essential metabolites that lie in pathways beyond the deficient enzymatic reaction also seems to ameliorate some conditions. For instance, treating patients having Type I and Type III glycogen storage disease (GSD) with 150 percent of the daily glucose production as a glucose infusion significantly reduced glycine turnover rates; less glycine was needed for gluconeogenesis. This therapy may prevent the growth failure of GSD that is caused by the consumption of protein stores in a futile effort to synthesize glucose.

In patients having bipterin-deficient hyperphenylalaninemia (a variant form of PKU), providing 5-hydroxytryptophan, dihydroxyphenylalanine, tetrahydrobiopterin and bipterin supplements has been successful. This form of PKU is due to a deficiency of dihydropteridine reductase (DHPR), an enzyme that provides a reduced bipterin cofactor needed to convert phenylalanine to tyrosine and tyrosine to dihydroxyphenylalanine (DOPA), and tryptophan to 5-hydroxytryptophan. In other cases of PKU due to a deficiency of phenylalanine hydroxylase, the enzyme needed to convert phenylalanine to tyrosine, it appears that providing tyrosine helps to promote proper growth and development. Tyrosine is needed for the synthesis of thyroxine, melanin and catecholamines as well as for protein synthesis.

The low phenylalanine diet for the treatment of PKU appears to be the most successful regimen for this frequent disorder. An important research question being explored, however, is at what age can a low phenylalanine diet be replaced with a normal diet. Intellectual and perceptual skills have been assessed in two groups of children with PKU who at age 6 were randomly assigned to either a low phenylalanine diet or normal diet: mean full scale I.Q. scores differed significantly (103 for those on the low phenylalanine diet and 98 for those on a normal diet). Blood phenylalanine levels >20 mg/dl were associated with declining IQ scores, while values <20 mg/dl were associated with rising IQ scores. In terms of reading and spelling achievement, small but significant differences were found in favor of the diet continued at age 8, but not at ages 9 and 10.

Diet therapy provided to pregnant phenylketonuric mothers appears to have various outcomes in the child ranging from mental normality with no evidence of fetal effect to neonatal death due to congenital heart disease. Available data support initiation of therapy prior to conception for best results.

Another relevant aspect of this research deals with the neuropathological basis for cerebral dysfunction in PKU. It seems from rat studies that high levels of phenylacetate, a metabolic product of phenylalanine, causes a decreased brain weight and alterations in the dendritic branching of pyramidal neurons in certain regions of the brain. In an experimental model of PKU and hyperphenylalaninemia, the administration of phenylalanine alone or combined with d-methyl-phenylalanine is being examined in terms of the effect on protein metabolism (i.e., phosphorylation and synthesis). Results have shown that cyclic AMP dependent protein kinase is decreased in the brain and phosphorylation of a specific ribosomal protein is inherited under these conditions.

Diet therapy and management of the urea cycle enzymopathies are also being tested. These inborn errors of urea synthesis occur about once in 30,000 births with infants unable to manage nitrogen metabolism, and therefore to carry out the metabolic steps required for normal growth and development. Investigators have reported successful results with therapies that use alpha-keto analogs of amino acids to stimulate nitrogen waste excretion. The keto analogs serve as amine group receptors and thereby reduce the amount of nitrogen excreted as urea; the keto acid analogs are transformed into essential amino acids needed for protein synthesis. D-keto-isocaproic acid, and the keto analogs of valine, isoleucine, methionine, and phenylalanine are now being used in this dietary therapy. The use of alternative metabolic pathways for excretion of excess ammonia and other nitrogenous metabolites are also being investigated; e.g., hippuric acid, phenylacetylglutamine, arginine or other components of the urea cycle such as citrulline or argininosuccinic acid may serve as possible endpoint alternatives to urea. A significant decrease in ammonium levels has been shown in patients with urea cycle enzymopathies by the oral administration of sodium benzoate which conjugates with glycine to form hippuric acid, and administration of phenylacetic acid which combines with glutamine and is excreted as phenylacetylglutamine. Infants treated prospectively have the best outcome and appear to have normal intellectual development.

Many people who live in the Mediterranean basin or in the malarial belts of Africa and Asia suffer from chronic hemolytic anemias caused by shifts in the intracellular redox potential. High doses of vitamin C appear to be successful in the treatment of the chronic hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency. In addition, vitamin E shifts the intracellular redox potential enough to ameliorate the oxidative environment caused by a deficiency of reduced glutathione which is caused by a deficiency of NADPH. Other investigators have also reversed the susceptibility of red and white blood cells to oxidative damage in patients with glutathione synthase deficiency with large doses of vitamin E.

Research of genetic-nutrient interactions in animal models aims to establish possible interactions of mutant and inbred animal models with trace

elements; to elucidate their mechanism of action; and to investigate the interaction of nutrients, genes and drugs. Manganese deficiency has been shown to depress the activity of superoxide dismutase (SOD), the enzyme which catalyzes the dismutation of superoxide free radicals and acts as an inhibitor in both reducing and oxidizing reactions. In one study, the activity of MN-SOD in the liver of manganese deficient mice was 17 percent that of controls, while activity in the brain was reduced by 50 percent. This decrease in MN-SOD activity causes an accumulation of free O_2 inside the mitochondria and may thereby explain the membrane damage, particularly in the mitochondria, caused by the manganese deficiency.

Investigators have delineated the effect of the mutant gene "crinkled" in mice on copper metabolism, and the relationship between dietary copper and the effects of the mutant gene "quaking". Liver CuZnSOD activity was lower in crinkled mice than in littermate controls at 14 and 60 days of age, while liver copper concentration was also low at 14 days but normal at 60 days. Data indicate that a high level of dietary copper supplementation during pregnancy and lactation increases CuZnSOD activity and copper concentration in the liver of mutant offspring to levels similar to those of littermate controls. Studies on the effect of copper supplementation on the "quaking" mutant (qk) mouse indicate that the postnatal period is the critical period for copper supplementation. This observation is consistent with the finding that the qk gene does not manifest itself until 10 days postpartum. Thus, copper supplementation during the prenatal period appears to have no beneficial result on the frequency of tremors, although it does help to treat the manifestations of Menkes kinky hair syndrome.

Analysis of the influence of combined genetic and nutritional factors on drug teratogenicity continues to improve our understanding of the interactions between genetic and nutritional factors in mammalian development. For example, high levels of dietary zinc may ameliorate the deleterious effects of 6-mercaptopurine on embryonic DNA metabolism and maternal toxicity. In addition, increasing levels of dietary zinc in the CBA mouse was found to reduce acetazolamide induced fetal malformations. This teratogen inhibits carbonic anhydrase by binding to the zinc ion at the enzyme's active site. The interaction between zinc and acetazolamide appears to be influenced by genetic background.

Research on the nonnutrient components of food, i.e., the intentional additives and the accidental chemical contaminants, explores the various facets of adverse biological effects associated with long-term low level exposure. Metabolic functions, interactions with cellular macromolecules, and mechanisms of toxic action are examined in order to assess mutagenicity and carcinogenicity risks of toxic substances in food. Investigations continue on the genetic regulation of aflatoxin metabolism, and the characterization of its precursors, pathogenesis, and mechanisms of carcinogenesis and toxicity. The common flavonols, quercetin and kaempferol, are being tested for mutagenicity in Salmonella typhimurium in order to determine the carcinogenic insult to intestinal epithelium.

Other studies on carcinogenesis, genetics and nutrition include: investigations on the specificity of amino acid effects on albumin synthesis and

of the regulation of amino acid synthesis in vitro under both metabolic and genetic control of hydroxylation rates; examination of the relationship of structural modifications of cell membranes with the cocarcinogenic action of cyclopropenoid fatty acids in diets with mycotoxins; and attempts to identify markers (e.g., restriction fragment length polymorphisms, sister chromatid exchange rates, and polyamine levels in breast fluid) specific for a cancer prone genotype in order to identify individuals at risk for cancer. One study of female breast cancer within disease-discordant twins evaluates demographic, environmental and medical histories of the twins and their families from registries in Denmark, Finland, Norway and Sweden. Familial clusters of cancer in the Mormon population are also being studied.

Additional studies of nutrition-related genetic disorders include research on hereditary diabetes, genetic factors in obesity and diabetes, genetic and hypothalamic obesity, the effects of dietary restriction in obese (FA/FA) rats, pancreatic polypeptide in the control of body weight, the physiological basis of polygenic obesity in mice, the role of beta endorphin in obesity, the pathogenesis of human cystinosis, and Cooley's anemia and iron storage disease, familial lipid patterns and coronary heart disease.

The San Antonio Heart Study is an epidemiological study assessing "diabetic pattern risk factors" (obesity, glucose intolerance, hypertriglyceridemia, and low levels of high density lipoproteins) in Mexican Americans. It is believed that as Mexican Americans acculturate to U.S. lifestyles that they will gradually lose their excess of risk factors.

Other studies of coronary heart disease, atherosclerosis, and familial lipid patterns are also under way. Investigators have found a decrease in the activity of cholesterol ester hydrolase (CEH) in the mononuclear cells of patients with symptomatic atherosclerosis, as well as in hyperlipidemic and diabetic individuals. The basic hypothesis being tested is that blood monocyte CEH activity may be predictive of intimal smooth muscle cell CEH activity. Therefore, decreased CEH activity increases the risk for progressive atherosclerosis due to the impaired cholesterol ester hydrolytic activity in the arterial smooth muscle cell. Patients with familial hypercholesterolemia, diabetes mellitus, and those who have had strokes or transient ischemic attacks are being studied. Another study is investigating the premise that metabolically active tissues can undergo a progression or regression of atherosclerotic plaques. Parameters being measured in patients on a low cholesterol diet and a typical U.S. diet include cholesterol turnover rate of both the free and cholesterol ester pools, the rate of cholesterol esterification, and the rate of cholesterol ester glycolysis in the arterial wall.

Epidemiological Research in Nutrition

Epidemiological research in nutrition examines the role of food habits and the socioeconomic factors that influence food selection in health and disease conditions. As a result, important relationships between diet and cancer, and between diet and cardiovascular disease have been revealed. Improved methods for assessing food intake and factors that influence food

selection also have been developed. In FY 1982, NHLBI, NCI, NICHD, NIADDK, NIDR, NIA, NIAID, DRR, NIEHS, and NEI supported projects with significant epidemiological nutrition research components.

The five basic categories of studies in this area include: 1) studies to evaluate methods and procedures used in epidemiological research in nutrition; 2) studies of nutrition's role on the physical and psychological development in defined populations; 3) nutrition-related epidemiological studies on maturation and reproductive functions; 4) surveys of nutrient intake and nutritional status assessment of special population groups; and 5) studies on the correlations of food intake to disease states.

Research on the effect of early nutrition on physical and psychological development, and maturation and reproductive function includes studies on correlates of adipose cell growth in infancy; the determinants of changes in fatness with age; the effect of environmental factors on childhood obesity; the effect of home-based behavioral programs on the treatment of obesity; the clinical correlates of vitamin D status in infants; the association of zinc deficiency with failure to thrive in infants; and the effect of diet and oral hygiene on caries development in school age children living in a fluoride free community. Studies of pregnant and lactating women examine the effect of folate deficiency on neural tube defects in the infant, the trends in breast and bottle feeding among groups of women in the U.S. and other groups such as the Pima Indians and the Negev Bedouins, and the effect of diet, alcohol and smoking on lactation and subsequent infant growth.

The antecedents and effects of breast and bottle feeding on infant growth and development are being analyzed also from data collected on 19,044 babies born to women pregnant between August 1959 to September 1966. Data collected on the mothers include socioeconomic status, educational level attained, smoking and drinking habits, drug and coffee intake, and obstetrical history.

An epidemiological study on the influence of diet to the age of menarche revealed no differences between a group of girls on strict vegetarian diets and those on a typical American diet.

Epidemiological studies on diabetes mellitus have been carried out in the Gila River Indians, Oklahoma Indians, and the Pima Indians. The longitudinal study of the Pima Indians examined the relationship between obesity in children and diabetes during pregnancy in their mothers. The study revealed that within each age group, the offspring of the diabetic women had much higher rates of obesity than the offspring of either nondiabetic or prediabetic women. This effect was seen regardless of maternal body-mass index and was observed throughout the period of observation. For example, at 15 to 19 years of age, 58 percent of the offspring of diabetics weighed 140 percent or more of their desirable weight as compared with 17 percent of the offspring of nondiabetics and 25 percent of those of prediabetics.

This study suggests that the excessive severity and frequency of obesity in the offspring of diabetic mothers is due largely to the abnormal

intrauterine environment and fetal overnutrition. The strong relation between the third trimester plasma glucose concentration and birth weight in the Pima population support the concept that the third trimester is an important period of intrauterine overnutrition. Thus, maternal diabetes during gestation may be one cause of obesity that may subsequently lead to diabetes in offspring. Controlling diabetes during pregnancy could be a first step in obesity and diabetes prevention in offspring.

An important component of the research carried out in this area includes cross-cultural surveys and case control studies that evaluate the relationship between nutrition and cancer etiology. Dietary exposures being assessed in human populations include consumption of specific food items and food groups (such as coffee, ethnic dishes, meats, fruits and vegetables) and macronutrient and micronutrient intake (such as fat, vitamin A, carotene, vitamin C, or folacin). These studies also investigate general nutritional status; anthropometry; biochemical indices such as serum cholesterol, serum vitamin A, or serum uric acid; and cooking practices. Cancers being studied include those of the colon, rectum, breast, esophagus, pharynx, oral cavity, lung, cervix, pancreas, stomach and kidney.

Studies are being carried out in targeted areas with unusually high mortality rates from cancers. For example, a case control study of esophageal cancer in black male residents of Washington, D.C. (the U.S. metropolitan area with the highest rate of esophageal cancer among black males) has shown that the consumption of meat and fish, dairy products and eggs, fruits and vegetables; the number of meals consumed each day; and relative weight (wt/ht) were each significantly and inversely correlated with the relative risk of esophageal cancer. None of the associations were markedly reduced by controlling for ethanol consumption, smoking, socioeconomic status, or other nutrition measures. Poor nutrition, in general, appeared to be the major dietary predictor of risk to esophageal cancer in this population.

A breast cancer study conducted in Alberta, Canada, where breast cancer rates are the highest in the world, suggests a significant increase in risk with the more frequent consumption of beef, pork, and sweet desserts. The study of oral and pharyngeal cancer among North Carolina women appears to suggest a protective effect of a diet high in fruits and vegetables. Additional case control cancer studies with a nutrition component include: lung cancer in New Jersey and in the Gulf Coast area of Texas; lung, pancreas, and stomach cancers in Louisiana; breast cancer in Israel; esophageal cancer in Charleston, Savannah and Jacksonville, Florida; urothelial cancer and prostate cancer in Hawaii; bladder cancer in Utah; leukemia and thyroid disease in Utah; and esophageal cancer in Iran.

In addition, studies are under way in special populations such as migrant workers whose changing cancer rates appear related to new lifestyles. Studies of migrant populations include three case control studies of colorectal cancer, one in persons of Czechoslovakian ancestry living in rural Nebraska, one in Mormons living in California, and the other of persons from the Northeast and North Central states living in the regions of Florida.

From the Nebraska study, the excess risk of colorectal cancer was primarily among persons with Czechoslovakian ancestry, particularly those from Bohemia and Moravia. The elevated risk among Bohemians was associated with diets high in fat and sweets and consumption of commercial beer, while the elevated risk among Moravians was associated with intestinal polyps and a familial history of gastrointestinal and other cancers.

Examination of the age-specific cancer mortality rates in three regions of Florida with high rates of immigration from the Northeast and North Central states has revealed that in these counties the colorectal cancer rates were as low as in southern counties of comparable populations and did not rise toward the northern rates at the older retirement age. This study will attempt to determine whether this reduction in risk is due to some change in lifestyle (e.g., diet or drinking water) or to the migrants being a self-selected healthy subset of northerners.

A prospective study of 120,000 women includes the collection of data on dietary intake practices, contraceptive practices, cigarette smoking, hair dye use, and pertinent demographic and gynecological histories. These data will allow the assessment of potential causal associations between breast cancer incidence and diet (i.e., intake of total fat, linoleic acid, trans fatty acids, saturated fat, cholesterol and caffeine); the determination of possible protective associations of retinol, carotene, vitamins C and E, and fiber; investigation of potential causal associations between fat intake, use of processed foods and the incidence of colon cancer; determination of potential protective associations between cruciferous vegetables, fiber, carotene and retinol, and vitamin C and colon cancer; and the evaluation of a potential protective association in smokers between the intake of retinol, carotene, vitamins C and E, cruciferous vegetables and the development of lung cancer. The protective or possibly causal associations of various dietary factors, artificial sweeteners, and alcohol use and the incidence of ovarian, uterine, bladder and skin cancer are also being considered.

Other prospective studies investigate heavy analgesic consumption, occupational exposures, cigarette smoking and coffee consumption in cancer of the renal pelvis and ureter.

One study of 21,900 male physicians between the ages of 50 to 75 years is under way to assess the chemopreventive effect of alternate day consumption of 30 milligrams (mg) of beta-carotene, as well as the effect on cardiovascular mortality of alternate day consumption of 325 mg of aspirin. Participants are randomized into one of four treatment groups: one 325 mg aspirin tablet every other day alternating with one 30 mg capsule of beta-carotene; one aspirin every other day alternating with one capsule of beta-carotene placebo; one aspirin placebo tablet every other day alternating with one capsule of beta-carotene; and one aspirin placebo tablet every other day alternating with one capsule of beta-carotene placebo. The incidence of cancer in this population will be assessed as well as cardiovascular mortality, coronary events, and total mortality.

A case control study under way in North Carolina evaluates the relationship of colon cancer and drinking water quality. Water quality indices

for the past 20 and 30 years are being developed based on water source, treatment and prior use characteristics, and will provide some insight on the importance of water borne carcinogens in the etiology of a known cancer site. Estimates of cancer risks at various exposure levels will be obtained.

Additional large-scale studies investigate dietary factors associated with coronary and vascular diseases. The Lipid Research Clinics (LRC) Program-Coronary Primary Prevention Trial that includes 3,810 subjects will come to a close after more than 7 years in August 1983. The data from the LRC Prevalence Study on lipid/lipoprotein distributions in 10 North American cities compare the prevalence of high lipid and lipoprotein levels in various age, race, ethnic and social groups. The Framingham Heart Study also investigated the role of diet on lipid and lipoprotein levels. The data indicate that in younger adults (20 to 50 years) alcohol consumption was highly associated with high density lipoprotein levels (HDL), while obesity and cigarette smoking were associated with all lipid fractions. Thus, in persons under 50 years of age, environmental factors are indeed associated with lipoprotein cholesterol profiles.

In terms of coronary heart disease morbidity and mortality, a number of investigators are studying the effect of alcohol consumption. A prospective study of 10,000 Yugoslavian men found a significant inverse relationship of alcohol consumption to coronary heart disease incidence even after accounting for differences in blood pressure, serum cholesterol levels, cigarette smoking and other variables. Since the protective effect of alcohol was absent for sudden death, it may reflect the deleterious effects of high alcohol consumption on the myocardial cells and increased vulnerability to lethal arrhythmias in an especially lean population.

In addition, of the 9,150 men who participated in the Puerto Rico Heart Health program, those who were moderate drinkers appeared to have the lowest incidence rates for nonsudden coronary death. The older and poorer members of this population, however, did not share in this benefit. Thus, it is premature to recommend moderate drinking as protection against coronary artery disease. Studies continue to examine the relative risk of myocardial infarction of moderate alcohol consumers and nondrinkers when HDL and other established risk factors are controlled.

Other studies examine the coronary risk factors in school age children in terms of familial dietary patterns and incidence of coronary disease, and the epidemiology of blood pressure. For example, 175 white children and 115 black children are being examined at ages 3, 4, and 5 years for blood pressure, heart rate, weight and height. This study will assess the age in different ethnic, socioeconomic, and sex groups that: 1) tracking of blood pressure and heart rate persists; 2) weight and change in weight is associated with blood pressure levels and 3) whether the level and distribution of blood pressure levels in families with infants having elevated blood pressure differs from families with infants having low blood pressure. Tracking of blood pressure has been demonstrated in children; i.e, children with high blood pressure continue to have high blood pressure over time. Multivariate analysis to examine predictors of tracking blood pressure will be made and thus help define appropriate strategies for primary prevention of hypertension.

The study of biological and sociocultural variables associated with blood pressure levels of 8,000 Japanese men living in Hawaii has been completed. From an analysis of more than 50 variables, it appears that obesity, age, hematocrit, heart rate, forced vital capacity, serum triglycerides, serum uric acid, cigarette smoking, and family history of hypertension are all independently associated with both cross-sectional levels and longitudinal changes in blood pressure. Among this cohort, milk intake was inversely associated with both systolic and diastolic blood pressure.

Nutritional Status

Research on nutritional status includes investigations to develop and evaluate various kinds of methods useful to determining the requirements of essential nutrients throughout the life cycle from fetal life to infancy, childhood, adolescence, adulthood, and the aged. Studies carried out in both normal and patient populations examine biochemical, anthropometric, maturational, and functional indices of nutritional status; methods to measure nutrient concentrations in various tissues and plasma; and dietary recall methods. The NIH is the major agency that supports research for the development of methods used in nutrition surveys. In FY 1982, research on nutritional status was supported by NICHD, NHLBI, NIADDK, NCI, DRR, NIGMS, NIDR, NIAID, and NEI.

Reliable methods for assessment of nutritional status are needed in order to: 1) determine whether or not impairment of health is the result of inadequate or inappropriate diet; 2) establish the specific nature of any nutritional problem underlying such health impairment; 3) provide knowledge on which to base dietary treatments for improving health; and 4) permit evaluation of the effectiveness of nutritional treatments or interventions that may be undertaken to improve health.

Methods to assess nutritional status include anthropometric measurements of weight and height, and skinfold thicknesses; biochemical measurements including assays for serum and tissue levels of various vitamins, minerals, fatty acids and amino acids; balance studies to assess bioavailability, absorption and metabolic status of trace elements, etc. Some of the specific methods being tested in the newborn include a prototype volume measuring instrument that consists of two chambers, a reference chamber and a measuring chamber that contains the infant. Infants fed various diets are placed in the chamber and the volume of each chamber is decreased cyclically; the pressure difference between the reference and the measuring chamber is determined with a differential manometer. Once perfected, this instrument will provide the first truly non-invasive means of assessing body volume changes in growing infants. Another noninvasive method for the evaluation of lean and fat mass in normal and premature newborn infants consists of an instrument that sets up an electromagnetic field which becomes perturbed by the introduction of electrolytes into the field. The degree of perturbation in the field is a function of the amount of electrolytes that reside almost exclusively in the lean body compartment.

Noninvasive techniques are also being used to provide additional insight on the metabolism and absorption of specific nutrients in the newborn;

for example, a number of carbohydrates (glucosamine, galactosamine, galactose, fucose, and sialic acid) are being analyzed for their contribution to the pulmonary excretion of gaseous hydrogen, ^{13}C labeled carbon dioxide and methane. This method is being used primarily to assess the status of the digestive and absorptive properties of premature infants, as well as infants with cystic fibrosis.

The bioavailability, absorption and metabolic status of calcium, iron, and zinc provided to premature infants in specialized formulas are being assessed through stable isotopes used in balance studies. Another component of this study includes examination of the transfer of these specific elements from lactating mothers to their infants. These studies help to assess the precise needs of the premature infant for trace metals in the diet, the best form in which to supply them, and the effect of the trace metal status of the lactating mother on the transfer of nutrients to the infant.

Zinc deficiency is a prevalent nutritional problem worldwide due to a high consumption of grains and cereals with phytate that bind zinc, as well as a number of diseases and disorders such as cirrhosis of the liver, sickle cell disease, prolonged hyperalimentation, and in states of malnutrition, etc. Since zinc deficiency appears to have a destructive effect on the immune system, a number of studies are under way to examine the interrelationship of zinc to the integrity of the immune system. Data from animal studies have shown that diets deficient only in zinc ($0.6 \mu\text{gZn/g}$) severely impaired delayed type hypersensitivity (DTH) to dinitrofluorobenzene (DNFB). Zinc replacement permitted normal DTH responses within 3 weeks. Examinations of whether the immune dysfunction is due to a uniform decrease in the number of lymphocytes or to selective decreases in certain subpopulations of these cells have revealed that: A) the T-cells vary in their sensitivity to zinc deficiency, and B) splenocytes show depressed responses to concanavalin A (50 percent), equivalent responses to phytohemagglutinin, and elevated responses in the mixed lymphocyte culture (100 percent) compared to control splenocytes. A marginal zinc deficiency in mice has also been shown to arrest growth and the development of their immune systems; responses to T-cell dependent (SRBC) and T-cell independent (dextran) antigens were reduced significantly in the deficient neonate.

The effects of zinc deficiency on skeletal and dental tissue has been recognized, especially in rats subjected to protein calorie malnutrition. The deficiency state is reversed when picolinic acid supplements at 0.2 gm/kg of diet are provided to the animals. Picolinic acid appears to aid the transport of zinc through the intestinal wall.

In addition, children with diabetes mellitus who also exhibit growth retardation and delayed sexual maturation may have excessive losses of zinc. Studies are under way to determine the zinc status of these children and to evaluate the effect of zinc supplements.

Another possible method to assess the zinc status in man is by monitoring the activity of RNAase, a zinc dependent enzyme. In a study of young adult men fed a zinc deficient diet for 8 weeks, this enzyme's activity

was increased significantly in the plasma and parotid saliva and returned to normal with zinc repletion. The zinc depleted men also exhibited leukopenia with relative lymphocytosis. In persons with impaired dark adaptation or night vision, zinc supplements were found to correct the impairment in adults not responsive to vitamin A. Tests used to assess dark adaptation as a functional measurement of vitamin A may therefore also be used to identify zinc deficiency.

Since early detection of hypovitaminosis A and the institution of prophylactic therapy can dramatically reduce the prevalence of xerophthalmia and vitamin A deficiency, a rapid dark adaptation test for use in the field is extremely important. A test which matches the color intensities of various discs to cone function rather than rod function has been developed and used with 95 percent sensitivity and 91 percent specificity. The test is based on the shift of retinal wavelength sensitivity as the eye dark adapts, and the need for the subject to separate sequentially the white and blue discs from a pile of red, white and blue discs. This test has been used satisfactorily with children aged 4 to 13 years under field conditions in Guatemala and in Baltimore.

Assessment of blood and urinary levels of vitamin A or its metabolites do not reflect tissue reserve stores until they become very depleted. A new method being tested to assess marginal states of vitamin A deficiency involves an oral challenge of small amounts of vitamin A and measurements of blood levels pre and 5 hours post dosing (the relative dose response, RDR). Such a method will allow persons in the field to identify for the first time marginal states of vitamin A deficiency.

A new method to study both the nutritional aspects of iron absorption and the movement of iron through the plasma has been developed. The "small dose iron tolerance test" involves the oral administration of 5 to 30 mg. of iron as sulfate or fumarate and the measurement of plasma iron concentrations at intervals for 8 hours. Persons mildly iron deficient exhibited significant increases in plasma iron concentrations during the first several hours, while the iron replete individuals had no changes in plasma iron. The iron tolerance curves vary with differences in total body iron status.

Assessment of nutritional status of obese and anorectic patients involve measurements of body composition and energy expenditure. One study of weight reduction in obese adolescents has revealed that a liquid protein diet of 500 calories per day, provided over a 34 to 48 day period, precipitated approximately 50 percent of the weight loss due to a loss in lean body mass. When this regimen is extended for an additional 4 months, the loss in lean body mass is reduced to 8 percent of total weight loss. It is interesting to note that with deliberate overfeeding for 3 weeks, approximately 40 percent of the weight gain consists of lean tissue gain. Thus, obese individuals appear to have significantly greater lean body mass than comparable nonobese subjects of similar stature.

Studies are under way to validate the double labeled water method for measuring energy expenditure; water made from the stable isotopes of ^2H and ^{18}O is administered and the ^2H lost in $^2\text{H}_2\text{O}$ and ^{18}O lost in $^{18}\text{CO}_2$ is

measured. This method will be compared with indirect calorimetry as a reference.

The use of nonradioactive stable isotopes have recently appeared to offer significant advantages over radioactive methods to assess nutritional status, especially of pregnant women and infants and children. Only small quantities of foodstuffs labeled with the stable isotopes of hydrogen, carbon, nitrogen, and oxygen are ingested, thereby making the procedure both noninvasive and cost effective. The technique also allows for interval measurements of enzyme activity.

A breath analysis test using the stable isotope technique to analyze carbon dioxide in the breath has been shown to be useful for measuring the rates of fat and carbohydrate absorption and metabolism. This test has been used to investigate the ability of a 1-month-old infant to utilize starch or corn syrup polymers when they replaced sucrose in the infant formula. Since the corn products are naturally enriched with the isotope of carbon used in the test, the appearance of labeled carbon dioxide in the breath demonstrated for the first time that a caloric benefit to the infant resulted from the ingestion of these complex carbohydrates. Analyses of fecal contents for the isotope confirmed that the starch was largely (more than 85 percent) absorbed. At least a portion of the starch is eventually scavenged from the colon as volatile fatty acid. This breath analysis test can be used to study normal premature infants, as well as infants with metabolic acidosis, acute diarrhea, and other problems.

Many studies also investigate the relationship of food intake, nutritional status, and functional performance especially in terms of reproduction, work performance and cognitive development. For example, the effect of marginal zinc or copper deficiency on spermatogenesis is being examined with atomic absorption techniques to establish the location of copper, manganese, zinc, and selenium within sperm cells. Zinc appears to be incorporated into sperm keratin that imparts structural integrity to sperm cells. Studies on the relationship of nutritional status to cognitive performance have broad implications in terms of school performance in undernourished children both in this country and abroad.

Maintaining an appropriate nutritional state is often difficult in the cancer patient whose metabolic processes bear the brunt of tumor insult, chemotherapeutic measures, and resultant anorexia. A study of cancer patients whose basal metabolic rates were evaluated by indirect calorimetry revealed that compared to controls, cancer patients were hypermetabolic. The basal metabolic rates, normal for surface area, were elevated for lean body mass. In addition, the malnourished cancer patients appeared to be deficient in anabolic hormones (growth hormone and testosterone), to have inappropriately elevated triiodothyronine levels, and to have excessive amounts of anti-insulin hormones.

Nutritional assessment methods for measuring adipose, musculoskeletal, cardiac, and visceral components of cancer patients with protein calorie malnutrition are being developed. Since measures of whole body counting using prompt gamma neutron activation (^{40}K and ^{14}N) provide clinicians

with an understanding of the effect of diet on muscle mass and other lean body compartments, studies are currently being carried out to look at the effect in cancer patients. The accuracy of computerized tomography (CT) scans in measuring limb, fat, muscle and bone volume has been standardized and evaluated in both normal and cancer patients. It appears that because the CT scan offers a rapid, reproducible, accurate, and non-invasive method of measuring the mass of internal organs and body composition that it has become an important technique for the evaluation and subsequent management of patients with malignancies.

A multi-institutional cancer study is under way to assess the efficacy of two levels of nutritional support in maintaining lean body mass by providing a constant energy supply. A number of investigations attempt to detect correlations and significance of clinical and laboratory estimates of nutritional status in order to gain a better understanding of the clinical relevancy of particular parameters. One investigator is performing kinetic studies on patients with gastrointestinal cancer in order to quantitatively evaluate energy expenditure and the composition of the diet mixture being burned. This research will provide information related to the amount and kind of nutritional support appropriate for cancer patients.

The appropriateness of various total parenteral and enteral nutrition solutions are being tested in patients with various malignancies; the nutritional status of these patients is compared to a normal population through the use of many nutritional assessment parameters. The long-range effects of nutritional support are being assessed by tolerance to chemotherapy, performance status, tumor response, and survival. In one study of nutritional support in metastatic colorectal patients, hyper-alimentation increased the rate of lactate production with a significant increase in carbon dioxide production. This study also revealed that increased basal lactate production and impaired glucose tolerance existed, independently of each other.

Research on the assessment of nutritional status in the patient population is also a priority of the Clinical Nutrition Research Units.

Investigations on the nutritional status of populations attempt: to determine whether specific health impairments, attributable to inadequate or inappropriate diet can be identified in a significant proportion of the population; to establish the nature of the dietary problem responsible for any such impairment; to provide information as to whether some action should or can be undertaken to remedy any present or foreseeable health impairment; and to evaluate any intervention that may be undertaken. A major research challenge is to improve the ability to differentiate between associations that are coincidental and those that are biologically significant as predictors of the health impairment under study.

A number of studies concerned with evaluating the effectiveness of dietary interventions on nutritional status and the risk for cardiovascular disease and hypertension are currently under way. For example, one of the intervention groups of the Hypertension Prevention Trial employs dietary restrictions, i.e., salt, in an attempt to control hypertension.

This trial also examines the correction of overweight as a treatment of hypertension. Another cohort of 8,000 Japanese men living in Hawaii was examined for factors associated with high blood pressure. Those factors shown to be independently associated with both cross-sectional levels and longitudinal changes in blood pressure were obesity, age, hematocrit, heart rate, serum triglyceride, serum uric acid levels, cigarette consumption and family history of hypertension. Other studies are examining the relationship of alcohol consumption to the incidence of coronary heart disease, morbidity and mortality.

In epidemiological studies and surveys of populations, nutritional status assessment measures include methods to screen individuals as well as to assess and monitor populations. When either an intervention program or survey is undertaken, standardized data collection and adequate data handling facilities ensure quality information that is available rapidly for analysis and utilization. Well documented data sets made available to agencies and scientists involved in studies of nutritional epidemiology will facilitate improvements in such studies.

An intervention project to assess dietary intake and nutritional status also requires data on food composition that accurately reflect the nutrients found in the food supply. Determining the reliability of food composition data is an ongoing process. Research must continue to be directed towards the development of improved methods of obtaining and analyzing food consumption data. Data on food consumption must also be integrated with information on health status, demographic characteristics, behavioral and particularly attitudinal measures.

Nutrition and Obesity

Obesity is a major health problem in the U.S., affecting both children and adults. Data from the NHANES I survey show that overweight affects a significant proportion of our population; 14 percent of the men and 24 percent of the women between ages of 20 to 74 years were found to be 20 percent or more above their desirable weight. One of every three women past the age of 55 is overweight. Similarly, data from the second NHANES (1976 to 1980) indicate that the prevalence of obesity persists and that those in the 90th percentile are even heavier than in previous surveys. Obesity is associated with hypertension, hyperlipidemia and hypercholesterolemia, diabetes, and osteoarthritis, and contributes to increased postsurgical infections and complications of pregnancy. It has recently been shown to be an independent risk factor for cardiovascular disease. Consequently, research on the biomedical and behavioral aspects of obesity is an important area of consideration at the NIH. DRR, NIADDK, NICHD, NHLBI, NCI, NIA, NINCDS, and NIGMS supported research in this important area.

Research is under way to examine the genetic, metabolic, clinical, environmental and behavioral aspects of obesity in humans and in animal models; to define the types of obesity; and to establish better methods of prevention and treatment. Studies of the developmental aspects of obesity, its natural history, and its heterogeneous origins attempt to identify determinants of obesity in infancy, childhood and adolescence.

Research on the natural history and development of obesity has shown that obesity during infancy does not predict obesity at 12 years of age, whereas obesity at 2 to 3 years for girls and 3 to 4 years for boys is a good predictor for adolescent obesity. No significant differences due to breast or bottle feeding were found in the obese and nonobese 12-year-old children, suggesting that obesity at 12 years of age may not be related to the type of infant feeding.

A longitudinal study of fat cell growth in infants has reported that fat cell size increases during the first 6 months of life and decreases from 7 through 55 months. Fat cell number, however, increases from birth through 55 months. In addition, infants fed at longer intervals had greater weight for height ratios than infants fed on demand. An inverse relationship between age at introduction of solid foods and infant weight for height ratios was also reported. Another investigator is examining the relationship between infant suckling behavior and growth indices in infants, as well as the relationship between physical activity levels and growth indices in young children between the ages of 4 and 8 years whose neonatal physical activity had been previously obtained.

Results of a large consortium grant assessing the natural history of obesity in 2,500 individuals between the ages of adolescence through the fifth decade indicate that fat cell number, total body fat and percent body fat increase in both men and women with increasing age. Women, however, have significantly more body fat and larger fat cells in their third decade, while men have more total body fat than women in the fifth decade. Of particular interest are the data indicating that obesity during infancy does not predict adult obesity, while obesity after four years of age does predict obesity in adulthood thus confirming the finding of a previous study described earlier in the report. Adolescent boys in the study appeared to have a near zero mean increment in total body fat, whereas girls had a positive increment with age. Total body fat in boys did not change significantly, whereas girls did experience a mean annual increase. Continuity between adolescent fatness and adulthood obesity appeared strong. In addition, familial correlations for obesity at the same chronological age are more similar for the first generation than for the second or third generations. Triceps skinfold measurements appeared as the best single indicator of percent body fat, and the ratio of body weight for height² (Body Mass Index - BMI) the best single indicator of total body fat.

Data on obesity from the Ten State Nutrition Survey and Tecumseh Study indicate that obesity falls along socioeconomic gradients and is most common in lower income females and median income males in both the black and white populations. The black female is generally fatter than the white female, however, at comparable levels of education, income or occupation both blacks and whites have comparable levels of fatness. Obesity also appears to follow family lines; that is, a child of two obese parents has greater than a 300 percent chance of becoming obese and at adulthood is likely to become over 300 percent fatter than a comparable child of lean parents. One fat sibling is likely to have another fat sibling about 40 percent of the time. The genetic hypothesis to obesity, however, appears challenged by husband and wife similarities in fatness,

as well as by similarities between adopted children and their parents. Fatness seems to be familial but not necessarily genetic; continuity of fatness levels appears to be as much a social or cohabitational effect as a biological effect.

Basic research on the pathogenesis of obesity includes studies on adipose cell morphology, thermogenesis, hypothalamic function, hormonal regulation, satiety signals, suitable methods for measuring body composition, and psychological factors underlying eating behaviors. Studies continue to examine fat cell size and fat cell number. Recent observations confirm the finding that extreme food deprivation does not alter fat cell number in the rat; i.e., adipocyte turnover was not evident following starvation using the radioactive labeled DNA precursor ^3H -thymidine.

Investigations of the genetically obese (FA/FA) Zucker rat have shown that with lateral hypothalamic lesions, the adipose cell number and size can be reduced to that of lean litter mates. When fed a diet that increased carcass lipids, neither the lesioned rat or the lean control showed any increase in fat cell number. In addition, the lean control rats maintained a higher body weight than pair-fed lesioned rats. The lesioned FA/FA rat, as well as the obese FA/FA rat, had elevated plasma insulin levels and reduced protein deposition with food restriction. It seems possible that lateral hypothalamic lesions affect a mechanism that sets the level of adiposity and possibly adipocyte number.

The working hypothesis of obesity which holds that hypothalamic pituitary dysfunction and altered neuroendocrine secretions cause decreased thermogenesis and/or increased food intake is under investigation. Changes in thyroid and catecholamine metabolism are being investigated. In studies of rats with ventromedial (VMH) hypothalamic lesions, the resting metabolic rate appeared to be 10 to 18 percent less than nonlesioned controls of similar body weight. Thus, the reduced basal energy expenditure in VMH lesioned rats suggests that the obesity caused by this lesion is due to an alteration in energy expenditure. Another study of VMH lesioned weanling rats examined norepinephrine turnover rates in various tissues as an indicator of sympathetic nervous system activity in relation to obesity. These rats had 38 percent less norepinephrine turnover in brown adipose tissue.

Brown adipose tissue (BAT) may have a very important role in the overall expression of the thermic effect of single meals in rats. The respiration rate of BAT differs with the nutrient content of the meal; i.e., the rate following a high carbohydrate meal is greater than after a high fat meal. Significant changes in the metabolic activity, amount and composition of BAT are apparent in response to single meals, therefore BAT and thermoreceptors in BAT may be linked to food intake control mechanisms. In studies of rats given diets of either sucrose, glucose, or fructose, and a standard diet, the rats given sucrose had the most BAT. Rats on any of the sugar diets had significantly more BAT than controls. Brown adipose tissue also appears to be important for the body's adaptation to the cold, and for metabolizing fuel to free energy when excess energy is consumed.

A number of factors known to control satiety are also being investigated. The satiety effect of bombesin (BBS) and cholecystokinin (CCK) appear to

be due to different mechanisms; e.g., abdominal vagotomy in rats abolished the satiety effect of cholecystokinin, but not that of intraperitoneal BBS. In baboons, small doses of BBS (1 ug/kg) reduced food consumption, slightly increased basal immunoreactive insulin (IRI), and suppressed postprandial increases of IRI. Additional studies of satiety in humans have shown that intravenous infusions of cholecystokinin-8 given to obese and lean men decreased food intake by 12 to 13 percent in both. Thus, obese men are as sensitive to the satiety effect of CCK-8 as lean men.

Research results also suggest that gastric distension per se is a potent satiety signal. In studies with rhesus monkeys, glucose intake was significantly reduced in those monkeys who after a 15-minute drinking bout had their stomach contents removed and refilled with non-nutrient saline, as compared to monkeys whose stomachs remained empty. Gastrin releasing hormone (GRH) also has been shown to elicit in rats the complete behavioral sequence of satiety and a dose-related suppression of meal size. Additional studies of rats given microinfusions of 5 thioglucose into the lateral or fourth ventricle of the brain suggest that the glucoreceptors that mediate feeding behavior and hyperglycemia in response to glucoprivation are located in the caudal hindbrain and not in the hypothalamus. Research is continuing in this area.

The influence of physiological regulators versus psychological drives on food intake is under investigation. The physiological control of food intake appears to override any psychological drive to consume highly palatable foods. This physiological control responds to changes in the palatability, caloric concentration, quantity of the food, etc. eaten on an average day. Increases in plasma glycerol levels, or glycerol in relation to free fatty acids, however, do not appear to reduce voluntary food intake in man.

Several metabolic and/or neural mechanisms may be involved in the maintenance of body weight and the maintenance of homeostasis with respect to specific metabolites. Overeating that leads to obesity could result from adaptive dietary responses to environmental "stress" within genetic capabilities. One hypothesis being tested is whether nutrient imbalances, toxicities or metabolic deficiencies turn off physiological appetite, while suboptimal but adequate levels stimulate the drive to overconsume energy. Studies on other possible causes of obesity have revealed that canine distemper virus and herpes simplex virus induced obesity when injected into young adult mice.

Due to the serious health implications of obesity, much of the research in this area attempts to uncover successful treatment measures that prevent its recurrence. In one study, individuals given 800 calorie diets differing in carbohydrate and fat lost similar amounts of lean and fat tissue with weight reduction. In addition, urinary calcium excretion was increased--presumably due to acidemia, which accompanies low calorie ketogenic regimens--thereby indicating the need to include sufficient carbohydrate in any hypocaloric regimen in order to prevent osteopenia. Studies on "protein-sparing" low calorie diets indicate that hypocaloric diets consisting only of protein do not spare more body nitrogen than an equivalent mixture of protein and carbohydrates. In addition, low calorie diets

consisting of protein and carbohydrate appear to maintain nitrogen balance and spare lean body mass much better than do isocaloric diets of protein and fat.

Studies in obese subjects made ketotic by starvation examine the effect of carbohydrate intake on the modulation of leucine oxidation and turnover. Results suggest that ketosis directly or indirectly enhances leucine oxidation; carbohydrate diets providing 300 to 800 kcals per day can prevent starvation induced ketosis, proteolysis and gluconeogenesis; the reduction of leucine turnover in starvation is most likely the result of reduced protein synthesis; and the nitrogen sparing effect of carbohydrate is in part due to a decrease in branched chain amino acid catabolism.

Other studies using a universal eating monitoring system examine the palatability of different diets modified to contain less energy. It appears that individuals eat fewer calories when a highly palatable diet is modified to contain less energy, suggesting that low calorie analogs are effective in promoting weight loss. Added fiber to certain foods has also been shown to be effective in reducing calorie intake and in subsequent weight loss.

Studies in rats on the effect of exercise on metabolism and subsequent weight loss indicate that exercise increases endogenous lipoprotein lipase and decreases intracellular triacylglycerols in the heart and skeletal muscle, thus lipoprotein lipase may be responsible for the intracellular hydrolysis of triacylglycerols in muscle during exercise.

Studies on the fat substitute sucrose polyester (SPE) indicate that SPE may be an effective agent for weight loss in obese subjects. SPE is a synthetic, calorie-free substance that cannot be absorbed by the digestive tract and looks, tastes, and smells like common dietary fats. One study of SPE included 10 chronically obese patients first fed a normal diet and then switched to SPE for dietary fat. An average of 60 grams of SPE replaced conventional fat in the altered diet which equaled a reduction of approximately 540 calories a day. Data from this study show that total calorie intake, which included meals and snacks, fell by 23 percent with the SPE diets. The subjects were better able to reduce their total intake of calories during the SPE period, while at the same time demonstrating appetite satisfaction. Snacks were not increased. The patients' average weight loss was approximately 0.4 pounds per day over 20 days. They demonstrated also a 10 percent reduction in total plasma cholesterol, a 14 percent reduction in low density lipoprotein cholesterol, and a 10 percent reduction in triglyceride level. Thus, sucrose polyester not only helps in weight loss, but, by virtue of its effect on plasma lipids, may also retard atherosclerosis.

Certain plant foods, such as kidney beans and wheat, contain a substance that inhibits salivary and pancreatic amylase. This anti-amylase has recently been purified, marketed for weight control under the generic name "starch blockers," and proclaimed to reduce the absorption of calories from starch. Studies have compared, by use of a 1-day calorie balance technique, the effect of starch blockers on calorie absorption after a high starch meal. The starch blockers did not inhibit the digestion and absorption of starch calories.

Studies have shown that behavior modification may be the most effective form of therapy for managing childhood obesity, especially if both the parent and child adhere to behaviorally oriented programs. After 2 years of followup, 100 percent of the children who had their parents participating in the weight loss program remained nonobese, while only 50 percent of those children participating alone maintained their nonobese state.

Another investigator examined the effects of behavioral modification on exercise in girls between 5 to 8 years of age. Earning a nonfood reward with an activity increased energy expenditure with exercise by 34 percent. Energy expenditure for the subsequent 90-minute period after the activity increased by 27 percent above the baseline post exercise energy expenditure. Children of thin mothers were able to do more work/kg of body weight than children of obese parents.

The relationship of obesity to disease states such as diabetes, coronary heart disease, cancer, stroke and hypertension is an important area of research. According to recent studies, individuals with fat distributed above the waist are more likely to develop diabetes than are those individuals who carry most of their excess weight in the hips and thighs. Men as a group and those women who are predominantly upper-body-obese are at the greatest risk of developing diabetes. Women with lower-body obesity have the least risk. Most of the excess weight carried by women with upperbody obesity is due to overpacked fat cells. Data suggest that variations in body chemistry determine the body's response to dieting, and perhaps the development of diabetes. Changes in eating patterns cause the enlarged abdominal fat cells in the upper-body-obese women to release fatty acids into the circulatory system. This influx of fatty acids might inhibit the use of glucose by body tissues causing the levels of glucose and insulin to rise, predisposing the person to diabetes. A contributing factor to high glucose and insulin levels may be also the small number of insulin receptors on the large abdominal fat cells of upper-body-obese persons.

A number of studies are investigating the relationship between obesity and hypertension, cardiovascular disease (CVD) and coronary heart disease (CHD). In the Hypertension Prevention Trial, overweight is a criterion to assess susceptibility to hypertension. Among hypertensives, blood pressure correlates with weight, and weight loss is usually associated with a decrease in blood pressure. A prospective epidemiologic study following 40,000 men and women for 10 years is evaluating the relationship of obesity, glycemia, physical activity and other traits--independent of the major risk factors to atherosclerotic cardiovascular disease.

A recent report of the relationship between relative weight and the long-term occurrence of CVD in the Framingham Heart Study cohort indicates that multiple logistic regression analyses show that Metropolitan relative weight (MRW)* on initial examination was related to the differences in

*The midpoint of the desirable weight range for medium build (Metropolitan Life 1959) was chosen as the reference weight for a given height. The MRW was computed for each subject by forming the ratio of his or her body weight to the reference weight for the particular height. This ratio is expressed as a whole number in percent.

the 26-year incidence of coronary disease, congestive heart failure, and coronary death in men, independently of age, cholesterol levels, systolic blood pressure, cigarette smoking, left ventricular hypertrophy, and glucose intolerance. Increasing relative weight in women was found to be associated with increasing coronary heart disease, stroke, congestive failure, and coronary and cardiovascular death. These data indicate that weight gain after the young adult years conveyed an increased risk of CVD in both sexes that could not be attributed either to the initial weight or the levels of the risk factors that may have resulted from weight gain. These results indicate the importance of obesity as an independent long-term predictor of CVD. In terms of mortality, the Framingham Heart Study data show a "U-" or "J-shaped" univariate relationship between total mortality from all causes and relative weight. Mortality rates rise well above the average at the underweight and overweight ends of the relative weight distribution. However, there is almost complete confounding of the effect of cigarette smoking and low MRW on mortality by the high proportion of cigarette smokers among the subjects with relatively low MRW. This study does support additional evidence that body weights in excess of those recommended as desirable by the 1959 Metropolitan Life Insurance Tables are associated with increased mortality. Thus, "slimmer is better" as long as underweight is not associated with a medical history of significant impairment and there is no evidence of calorie, protein, vitamin or mineral deficiency.

A recent study in obese subjects has shown that obese men overproduce low density lipoprotein (LDL), the most atherogenic lipoprotein. This metabolic abnormality could be the cause of increased risk for CHD in obesity. In addition, diet induced hyperlipidemia is being studied in nonhuman primates. Obesity, hypertension, cigarette smoking and behavior are the risk factors being studied for their modulating effect on diet-induced atherogenesis.

In studies of obesity and cancer, research is under way on the effects of high and low fat diets, reduced calorie intake, and hypothalamic induced obesity on serum hormone levels and the subsequent development and growth of breast tumors. The overall objective of this research is to determine the brain's role, particularly the hypothalamus, in the development and growth of mammary and pituitary tumors and to utilize this information to inhibit such development and growth.

Nutrition Education Research

Research to uncover better methods to educate persons on the role of nutrition and diet in health and disease involves a number of intervention programs and clinical trials supported by NHLBI, NICHD, AND NCI.

A number of projects to determine appropriate nutrition education methods for children and their parents are included in this special interest area. One study is testing the effectiveness of various processes to measure conceptual knowledge of food and nutrition among preschool children. Discrimination and puzzle solving tasks appear to be effective techniques for measuring knowledge of food and nutrition, whereas free word association techniques do not. Findings from this study will be used to develop a

nutrition education program aimed at decreasing sugar consumption and increasing consumption of nutrient dense foods.

Another project on the development of positive health behavior in preschoolers investigates the antecedents of positive and negative health behaviors early in childhood with the aim of producing an effective health education program that will have a lasting effect on adult health behaviors. The group of 3- and 4-year-old children who receive nutrition education intervention twice a week will have their health behaviors assessed yearly for 2 years after the intervention in order to determine any effect on dietary knowledge and behavior. The baseline data on the antecedents for adult health behavior are also being used to design educational programs for the parents.

The causes, prevention, and treatment of obesity in children is an important research issue. As a result, nutrition education research projects attempt to develop appropriate behavior modification methods that may prove useful. One project that evaluates early family environment and parent/child interactions in regard to food and eating will provide a model teaching base for students of various disciplines who are involved in the care and education of overweight and obese children. Another project is designed to ascertain whether the teaching of eating or exercise behavior should receive the most emphasis in a home-based behavior program. A study to determine the effectiveness of training parents to implement behavior techniques designed to regulate their obese children's eating and exercise habits has demonstrated that parents can indeed be trained to implement a behaviorally-based program to improve eating and exercise habits.

A related project is developing and evaluating a behavior modification program for families of obese children that consists of a program to train parents in general child management skills, and encourages behavior modification by the parents, even though the obese child is the target of the intervention. Other studies are evaluating diet management strategies for overweight children, as well as those for obese children with Prader-Willi syndrome. Sucrose induced behavior changes are also being measured as part of the latter program.

A study entitled "Infant Feeding Problems Today: Implications for Nutrition Education" interviewed mothers of 1-year-old infants to determine the mothers' exposure to nutrition information and its relationship to their feeding choices. Results of the study indicate that breast-feeding mothers are more inclined to follow the advice of friends, classes, and literature. Pediatrician's advice was followed most carefully by mothers who fed formula to their babies, who introduced solids before age 6 months, or who had low-birth-weight infants. Data on how infant feeding practices relate to growth indicate that weight and length measurements of breast and formula fed infants were similar.

Another project involves developing teaching materials for independent instruction in basic nutrition facts and testing the efficacy of programmed nutrition educational packages. Data collected thus far indicate that this method is effective in teaching facts but not in guiding students

in the practical application of these facts. A project entitled "Nutrition Education Via Telecommunications Satellite" is designed to compare the effectiveness of the following three methods of nutrition education for health professionals: videotapes plus regular classroom discussion sessions; videotapes and structured discussion via satellite; and videotapes and informal off-campus discussion sessions. Results from the study show that students involved in formal discussions with instructors either in the classroom or via the satellite demonstrated similar learning and satisfaction with the learning experience. Those students without access to instructors performed reasonably well, but were much less satisfied with the course and its content. From this study, it seems that some personal contact, either directly or by satellite between students and instructors, is desirable for a successful and satisfying nutrition education program.

A number of intervention trials dealing with hypertension control have a nutrition education research component. The Dietary Intervention Study of Hypertension (DISH) is a collaborative study of the effect of dietary modification, i.e., nutrition education for weight reduction and sodium control on blood pressure levels. DISH has a goal of determining what percentage of hypertensive patients who had been treated for 5 years would be adequately controlled after antihypertensive medication, under the following circumstances: (1) withdrawal of medication, no dietary management, (2) withdrawal of medication, decreased sodium intake/increased potassium intake, (3) withdrawal of medication, weight loss, or (4) continued stepped (medication) care. Data analyses indicate that the highest success rates were in the obese weight-reduction group (59.5 percent) and the sodium restricted group, who had thin body weight status.

Another study on the nonpharmacologic control of hypertension examines the feasibility of withdrawing medications from "mild" hypertensives and maintaining satisfactory blood pressure using only weight control and sodium restriction regimens. Preliminary data suggest that blood pressure control can be maintained in a high proportion of these individuals with little or no medications, especially with weight reduction and decreases in alcohol and sodium intake.

Dietary measures to control or prevent hypertension are also being studied in hypertensive prone individuals. A feasibility Hypertension Prevention Trial has enrolled 800 men and women between 25 to 50 years of age with high/normal diastolic blood pressure. Several intervention efforts employing dietary means to control hypertension are being examined for their success in obtaining decreases in weight, salt intake, and blood pressure.

Two demonstration and nutrition education research projects related to hypertension are under way at the New Jersey Medical School; one will explore the possibility that dietary change and/or relaxation training will reduce or eliminate the need for medication in a hypertensive population. The second project is testing the hypothesis that nonpharmacological treatment for hypertension can be carried out largely by paraprofessionals and in nonclinic settings, such as the workplace and in community sites. Another demonstration and education study on hypertension includes five family practice centers located in demographically

diverse communities in Virginia. Behavioral education programs directed at high risk patients/families will be assessed in terms of an appropriate reduction of salt intake and smoking cessation.

A number of community demonstration studies attempt to produce significant changes in health behaviors associated with cardiovascular risk, thereby reducing excess morbidity and mortality associated with cardiovascular disease. Some of these programs emphasize the mobilization of existing community resources while others attempt to establish new programs and activities. These studies provide information on enhancing program continuity, in addition to data on cardiovascular risk factor reduction.

Three community based programs testing the hypothesis that cardiovascular disease (CVD) risk factors can be changed and maintained through community organizations and education strategies include the Stanford Health Disease Prevention Program, the Minnesota Heart Health Program, and the Pawtucket Heart Health Program. The Stanford program involves media campaigns with publications on blood pressure control, television spots on weight reduction, and a multimedia smoking cessation program. The Minnesota program is testing various strategies to lower CVD morbidity and mortality in three communities in the upper Midwest. The Pawtucket program examines changes in the CVD risk factors with a high level of professional and organizational assistance versus a low level of professional assistance. The risk factors being considered are blood lipids, blood pressure, smoking, obesity, and physical fitness.

A 5-year study currently under way is designed to modify cardiovascular family risk through a tailored intervention program for families, a school screening program a high school level cardiovascular curriculum, and a parent education program. This intervention program will attempt to demonstrate greater gains in CVD risk factor reductions for those persons with a positive family history of CVD.

Results from the nutrition education program, Foods for Health, sponsored by NHLBI and Giant Food Inc., reveal that it achieved its main objectives of communicating nutrition information to the consumer, determining the feasibility of implementing and evaluating a point of purchase program, and creating interest and awareness about nutrition in outside business organizations. Data on the mean adjusted correct responses to the nutrition knowledge questions revealed a greater gain in correct scores for the Washington study population where the intervention occurred as compared to the Baltimore control group; i.e., a gain of 10 percent for questions on the fat/cholesterol content of foods and a gain of 6.8 percent for those on the relationship between dietary fat and serum cholesterol. These scores were associated with sex, education, age and having a family member on a special diet. In general, females from the Washington population had a higher percent of correct responses, and Washington respondents had higher reported educational levels. The weekly sales of specific food items were monitored in order to detect any change in sales in relation to the nutrition messages made in Washington and Baltimore, respectively. No apparent differences in food sales could be attributed to the nutrition education intervention.

The CNRU's are also a significant focus for nutrition education research since their mission is to combine research, patient care, and public education activities, often in the form of community outreach programs.

Examples of the research under way at the CNRU's include projects to evaluate the effectiveness of various in-service programs with basic nutrition information, and to develop innovative teaching tools for children with juvenile diabetes that can be adapted to each child's age and preferred learning mode. Research to develop nutrition education programs useful to fostering proper nutritional habits in children and adults, both professional and nonprofessionals, is an important undertaking of the CNRU's.

Total Parenteral and Enteral Nutrition

Appropriate nutritional support for those individuals unable to ingest, digest, or absorb foods is essential in order to permit normal growth, development and maintenance of health. Research continues therefore to examine and define the special nutrient needs of patients requiring total parenteral or enteral nutrition. DRR, NIADDK, NIGMS, NICHD, NCI, NIA, NHLBI, NIAID, and NINCDS supported nutrition research in this area.

Research on the parenteral requirements for amino acids in premature infants of various gestational ages indicates that the requirement for each amino acid is defined as that amount that produces a serum concentration within 95 percent confidence limits of the 2-hour postprandial serum concentrations observed in normal infants. In addition, the quality (fat versus carbohydrate) and quantity of the parenteral caloric supply to premature infants is being examined in terms of nitrogen retention. Newborn hyperglycemia induced by parenteral therapy, as well as the metabolism of intravenously administered lipid emulsions are also being studied.

In one study of neonatal hyperglycemia, investigators have found that low-birth-weight premature infants manufacture their own glucose even during constant glucose infusion. Infants weighing less than 1000 grams (26-29 weeks) all had glucose production rates less than 3.5 mg/kg/min. The more immature the infant, the lower the glucose turnover rate. These findings indicate that impaired utilization of glucose may be the major determinant of hyperglycemia in premature infants who receive parenteral glucose infusions. Plasma glucose levels ranged from 67 to 173 mg/dl and glucose production rates from 0.14 to 22.3 mg/kg/min.

In order to assess whether differences in the energy intake of premature infants primarily influence the rate of weight gain or the body composition of gain, one study is feeding two groups of infants equal volumes of formula with the same protein concentration, but different energy densities. Preliminary data suggest a similar rate of gain in both groups, thereby suggesting differences in the body composition. The investigators hypothesize that the higher energy intake will lead to a greater fat content of weight gain, and consequently a greater energy cost of growth.

Studies of lipid clearing in parenterally fed pre-term infants are measuring the activity of extrahepatic and hepatic-derived serum post-heparin lipolytic activity. Since heparin-released lipase activity is a

direct indicator of total lipid activity, a decrease in lipase activity may potentiate the slower clearance of intralipid found in very low-birth-weight infants.

In terms of studies on enteral nutrient therapy in infants and children, the efficacy of nocturnal enteral glucose therapy in children with glycogen storage disease is being investigated. As a substitute to the current therapy of giving frequent high carbohydrate feedings during the day and a constant nocturnal nasogastric drip of glucose, investigators are looking at the effect of corn starch given every 6 hours. Thus far, they have demonstrated improved control of the aberrant metabolic status.

In order to understand the mechanism of food protein intolerances in infants, intestinal epithelial events (developmental changes in intestinal permeability to protein) are being examined in infants enterally fed lactose. It is hypothesized that lactose in breast milk is required as a source of galactose for glycosylation of epithelial glycoproteins and glycolipids. Studies in rabbits have shown that lactose concentration in milk and mucosal lactase activity in suckling rabbits correlates with the intestinal epithelium sensitivity to ricin, a toxin similar to soy protein lectin that binds to galactose residues. Lactose in breast milk, through its role in membrane glycosylation therefore may exert an influence on mucosal uptake of milk proteins, as well as on trophic hormones such as insulin and epidermal growth factor, and on membrane stability.

Additional studies in infants consider the effect of cysteine and taurine in TPN given to infants; the metabolic fate of fat emulsions; and the amino acid and nitrogen balance with varied protein and energy intakes.

Studies on amino acid and nitrogen balance indicate that the branched chain amino acids, leucine, isoleucine and valine serve as biochemical regulators and precursors in such metabolic reactions as cholesterol synthesis, protein turnover in skeletal muscle, oxidative energy metabolism in muscle, gluconeogenesis, insulin secretion and urea formation. These amino acids therefore are being studied in the treatment of protein wasting found with trauma and sepsis, and hepatic encephalopathy. Data indicate that the effect of leucine and its keto analogue alpha keto isocaproic acid on protein conservation and protein synthesis may prove helpful in the treatment of portal-systemic encephalopathy, renal disease, diabetes, and trauma.

Studies of the nutritional support of patients, especially those with trauma and burns, have shown the benefit of providing 25 percent of the calories as protein and the need for first meeting the caloric requirement. It seems that malnutrition is the major contributing factor to the defects in phagocytic function leading to infections in such patients. In addition, severe opsonic deficiencies magnify these adverse defects. These patients also have an increase in glucose production and glucose flow with adequate insulin, as well as a sustained hypermetabolism and negative nitrogen balance causing severe weight loss. The underlying mechanisms of these changes and the necessary nutritional support to sustain life in these patients continues to be investigated.

The nutritional support of cancer patients is an important area of research which tests the hypothesis that the administration of TPN is more effective than normal hospital regimens in maintaining adequate nutritional status and that it does not adversely affect tumor control. A number of clinical studies as well as animal studies attempt to assess the effectiveness of TPN in maintaining the immune response and thereby lessening or moderating the complications associated with cancer treatment.

In animal studies, the hypothesis that a tumor induced amino acid imbalance is responsible for some of the tumor's effects on the host is being investigated through the administration of five parenteral diets containing different amino acid mixtures.

In addition, prospective trials of the use of TPN as an adjunct to radiation, surgery and aggressive chemotherapy are under way. One study is evaluating the benefits and complications of nutritional support to children receiving multimodal treatment for stages II to IV Wilms' tumor. Other studies examine the importance of nutritional rehabilitation in head and neck cancer, the efficacy of multimodal therapy in operable esophageal carcinoma, and the prevention or reversal of malnutrition in neuroblastoma.

The prolonged use of some total parenteral nutrition solutions has been shown to lead to such complications as bone disease in some patients. They appeared to have deficient serum levels of parathyroid hormone and the active vitamin D metabolite, as well as excessive urinary calcium excretion. Data has shown that reducing concentrations of calcium and protein led to decreased calcium excretion. More research on the mechanisms involved in metabolic bone disease is warranted.

Maternal Nutrition

The nutritional status of the mother affects the growth and development of her child, as well as her own health and well-being. NICHD, DRR, NIADDK, NIDR, NHLBI, NIAID, NINCDS, and NCI supported this research.

Research in this area includes studies on: the relationship of maternal nutritional status to reproductive function; nutritional requirements of women during pregnancy and lactation; the relationship of maternal nutrient intake to fetal outcome and subsequent infant growth and development; placental transport of nutrients from maternal to fetal circulation; the causes and potential nutritional therapy for intrauterine growth retardation; and the various components of human milk.

Since a reduction in the dietary intake of energy and/or protein during pregnancy has been shown to be associated with fetal growth retardation, a number of longitudinal studies have attempted to ascertain the optimal nutrient requirements of the maternal-fetal unit. In addition to requirements for energy and protein, the requirements for vitamins, minerals and trace elements are under study. Data on the requirements for vitamin A, for example, reveal that maternal vitamin A serum levels fluctuate and vary with intake, but the exact mechanisms of control of these levels, placental transport, and fetal utilization of the vitamin remain unknown.

Placental transport of vitamin A increases when the maternal stores are low, while high maternal stores suppress transport. Fetal metabolism of retinol appears to be specific and somewhat different than that of the mature animal. Quantitative determinations of retinol metabolism and kinetics in the maternal-placental-fetal system will facilitate the estimation of maternal, fetal and neonatal requirements and aid in the prevention of fetal losses and neonatal disease associated with inappropriate vitamin A intakes.

Vitamin A in excess or deficient quantities early in the gestation of animals has been shown to cause anomalies that frequently involve the eye. The form of vitamin A transferred to the developing fetus of different gestational ages, its deposition in various fetal tissues including the eye, and the mechanism of placental transport are being investigated in rats. This research will provide insights into the influence of maternal vitamin A status on normal fetal development of ocular tissue and on subsequent visual function.

Since vitamin A transport, storage and utilization are highly dependent on protein, the study of vitamin A metabolism in the maternal-fetal neonatal unit also includes examination of the effects of protein intake. Dietary levels of vitamin A significantly affect protein metabolism, thus the protein requirement may vary depending on the vitamin A intake. Moreover, the vitamin A requirement is likely to vary with protein intake.

A rat model is also being used to study the degree of fetal growth that can be supported from maternal lean tissue catabolism. Studies of 24-hour 3-methyl histidine excretion have shown that maternal muscle tissue breakdown is a function of maternal diet, and that the metabolic needs for fetal growth are not met from maternal muscle tissue breakdown.

The means by which nutrients pass from the mother and her fetus are indeed complex. The placenta must provide the human fetus in late gestation with 10 mmoles/kg/day of amino acids for tissue anabolism, 20-25 mmoles/kg/day for nitrogen catabolism and 40 mmoles/kg/day of glucose. Studies on the mechanisms responsible for the net transfer of these large quantities of nutrients have revealed that the mammalian placental microvillus membrane capacity for glucose uptake exceeds fetal needs by a factor of sixteen. In addition, a glucose transport protein, with a molecular weight of 52,000 and associated with actin, has been identified to mediate the transport of glucose from the mother to the fetus.

Other research has shown that in late gestation, approximately one-third of the maternal glucose production is utilized by the placenta and a lesser amount by the fetus. In response to maternal hypoglycemia of fasting, the conceptus (placenta plus fetus) reduces its utilization of maternal glucose and increases the production of endogenous glucose. However, the decreased utilization of maternal glucose is associated with decreased fetal growth.

Iron transfer across the placenta is also vital for fetal growth. During pregnancy, the fetus accumulates large amounts of iron in order to support erythropoiesis, and maternal iron must be actively transported against a

trans-placental concentration gradient. Investigations using a guinea pig model have shown that ferric placental iron moves from the maternal to the fetal circulations by passing through endothelial cell junctions, possibly with a low molecular weight carrier protein; maternal transferrin releases iron at the cell surface and does not cross the placenta; and fetal iron does not cross the placenta into the maternal circulation but regulates the transport of maternal iron into the fetal circulation.

Studies on calcium placental transport have isolated and purified human placental-calcium binding protein (HCa BP) with a molecular weight of 150,000 and 27 percent acidic residues of aspartate and glutamate. HCa BP is saturable at concentrations of Ca^{++} above 4 mM; cellular localization studies have shown that the calcium binding protein increases in concentration during gestation and is primarily associated with the maternal face of the chorioallantoic placenta and the uterine wall.

In general, fetal needs for specific levels of nutrient substrates can be met by the usual ranges of the nutrients encountered in the maternal-placental circulation. Studies, however, are investigating fetal growth and nutrient requirements that take into account the differential genetic composition of mother and fetus. Genotypic exigencies dictate fetal demands for nutrients such as copper, manganese, pyridoxine, and biotin that exceed the maternal-placental circulation supply. Deleterious fetal development can be avoided if the nutritional demands of the aberrant genotypes are met by augmenting the maternal diet with specific nutrients. The basic discovery in the realm of intrauterine-genetic-nutrient interactions paves the way for nutritional therapy during fetal life for certain inborn errors of metabolism and other kinds of extreme nutrient dependency. Diseases which have been fatal in the untreated newborn can be transformed into a harmless condition by safe and effective treatments prior to birth. Such treatment obviates the need for prenatal diagnoses and its attendant risk to the fetus.

Research continues on elucidating predictors of intrauterine growth retardation (IUGR) which affects approximately 100,000 pregnancies per year in the U.S. Its etiology is multifactorial in nature and involves maternal nutritional status and maternal nutrient intake during pregnancy, placental circulation and nutrient transfer, maternal smoking and socioeconomic status, and maternal fetal endocrinological status.

The role of polyamines in the maternal circulation as physiological indicators useful to differentiate normal and abnormal pregnancies is being investigated. Polyamine levels increase in the amniotic fluid as a function of gestation, presumably as a reflection of rapid fetal growth. The analysis of the amniotic fluid polyamine levels may provide an important marker for fetal problems such as IUGR.

An ovine model of IUGR by induced placental insufficiency or by maternal dietary restriction (20 percent of required protein and 50 percent of required calories during the third trimester) is being used to investigate differences in fetal body composition resulting from IUGR. Another ovine model has shown that infusion of a 4 percent glucose and 6.8 percent amino acid solution directly into the fetal stomach during the period of

maternal dietary restriction significantly increases birth weight and crown/rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. These investigators have also shown that during maternal dietary restriction, the upper body of the fetus receives substantially greater blood flow than the lower body which may be important in protecting growth of upper body organs (brain and heart). Research to test intrauterine nutritional therapy in humans will likely be forthcoming.

Research on infantile respiratory distress syndrome (RDS) is also a priority since RDS is the single most frequent cause of death during the neonatal period. A small but important fraction of the risk deals with the nutritional status of the mother, which along with steroid therapy is being studied as a possible means of reducing the risk of premature birth and consequent risk of RDS. Other studies investigate maternal protein intake and mental retardation in the newborn, as well as the effect of dietary deficiencies and ethanol intake on neural development.

In terms of the impact of disease states or conditions of women on the fetus and newborn, studies continue on maternal phenylketonuria, diabetes in pregnancy, pica, and pregnancies complicated by hypertension and renal disease.

Factors affecting lactation and immune properties of human milk are under study in order to establish the best possible conditions for infant feeding. The effects of diet, smoking and drinking on lactation are being investigated as well as the bioenergetics of fasting and lactation.

Additional highlights on human milk research are included under the special interest area on "Child and Infant Nutrition Research."

Nutrition Education for the Public

An integral part of the NIH nutrition program is the translation of research results into practical information for the public. The NCI and NHLBI have specific mandates for information and education. In addition, work is supported by NIADDK, NICHD, NEI and the Nutrition Coordinating Committee office.

Nutrition information is disseminated through specific NIH publications and fact sheets available from the various Institutes' information offices, Public Service Announcements (PSAs), the NIH lecture series "Medicine for the Laymen," films or videotapes, and responses to public inquiries. In FY 1982, the nutrition publications available to the public included: Questions about Weight, Salt and High Blood Pressure, Fact Sheet Hyperlipoproteinemia, and various "Eater's Almanacs," (NHLBI); "NIA Age Page: Food: Staying Healthy After 65," (NIA); "Food Allergy," (NIAID); and "Snack Facts," (NIDR). The USDA/DHHS publication, Nutrition and Your Health, Dietary Guidelines for Americans, is also available to the public from the Consumer Information Center, Pueblo, Colorado.

One public service program, entitled "Living with Aging" and done in collaboration with the NIH and Peoples Drug Store, is providing the elderly and their families with important health promotion information.

"Food for Life After Age 65" and "Taking Care of Your Teeth" are two of the eight free brochures that are being displayed in all of the Peoples' 525 drug stores in 14 states and the District of Columbia. These brochures, designed and printed by the drug store, are based entirely on the existing Age Page publication by NIA. The first draft of a new Age Page on "Dietary Supplements" has been prepared and will be available in the near future.

Two new nutrition publications soon to be available to the public are "Facts About Nutrition," a publication of general nutrition information on the various nutrients, i.e. their functions, requirements, etc., and "Facts About Obesity," a publication that explains obesity in terms of causes, prevention, and appropriate treatment. These publications will be available from NIADDK.

A collection of articles about NIH research developments is compiled by the NIH Office of Communications in the publication entitled NIH News and Features, which is made available to various members of the press and scientific journalists, as well as the general public. Approximately 8 to 10 percent of its content contains nutrition research activities and highlights. The NIH lecture series "Medicine for the Laymen," now in its fifth year, included a lecture on "Behavior Patterns and Health." This lecture examined six common lifestyle factors--dietary patterns, exercise, alcohol use, cigarette smoking, stress and sleep patterns--and their relationship to health and diseases, such as heart disease, cancer, stroke, diabetes, etc. This series is videotaped for possible use on public television.

A number of studies are under way to evaluate the various means of educating certain segments of the general public about different aspects of nutrition. These studies include investigations to determine the effectiveness of various procedures to measure conceptual knowledge of food and nutrition among preschool children, to develop a comprehensive health education curriculum stressing health behaviors in preschool children, and to train parents in ways to manage their children's nutritional intake. It seems that children of parents who had received additional child management training maintained their weight loss better than other children. These projects are described in more detail under the special interest area on "Nutrition Education Research."

Nutrition education and information programs are also integrated into various cancer and heart disease education programs. Efforts are under way to educate the public on the role of diet and nutrition in cancer etiology and prevention, as well as in the treatment and rehabilitation of the cancer patient. The Diet, Nutrition and Cancer Program, NCI, has developed and distributed a number of pamphlets and handbooks to advise cancer patients on the role of nutrition and cancer therapy. Work with the Candlelighters also continues in order to develop resource material for the child with cancer. Community based programs that educate the public on cancer also include nutrition information as a major component.

Programs also continue to translate fundamental research results in heart disease into practical suggestions. The role of nutrition in good heart health was explicitly stressed in the "Foods for Health" program initiated

by NHLBI in cooperation with Giant Foods in FY 1978. Supermarket shoppers received free information on the relationship of diet and coronary heart disease through publications known as "Eater's Almanacs." Requests to reprint the almanacs continue to be received in FY 1982. The final report on this project has been completed and the findings are described in the special interest area on "Nutrition Education Research."

The NCC and the NCC Subcommittee on Nutrition Education again in FY 1982 served as consultants in the production of the sequel "Eat Well, Be Well II," produced by Amram Nowak Associates under a contract with the Metropolitan Life Foundation. This sequel included cooperation from government, industry, and the scientific community in a nutrition education endeavor. It is described in detail on pages 115-16 of this report.

In addition, the Subcommittee on Nutrition Education developed a comprehensive program of nutrition activities that were carried out at the NIH for all employees during National Nutrition Month, March 1982. As part of these activities, it conducted a nutrition education workplace intervention project which was described in detail in the FY 1982 Program in Biomedical and Behavioral Nutrition Research and Training as part of the subcommittee's FY 1982 activities.

Another service provided by all the Institutes and by the NCC is the handling of public inquiries, both by mail and telephone. Information specialists are available during working hours to answer any questions--lay or professional--not only on nutrition, but also on all research topics within the purview of the NIH. In addition, the NCC maintains a full-time office staff to provide support to the committee and to serve as a focal point for nutrition information. The NCC office responds to inquiries from the scientific community, the media, and the concerned public.

Nutrition and Aging

Nutrition is certainly one of the influential environmental factors that exert chronic influence on the aging organism. Much of the research on nutrition and aging considers whether nutritional needs change significantly beyond the middle decades of life and, if so, what specific nutrients are involved. In FY 1982, NIA, NHLBI, NEI, NIADDK, DRR, NINCDS, and NCI supported research in this area.

Laboratory and clinical studies are under way to examine the effect of aging on nutrient requirements, absorption and metabolism, as well as the effect of diet on the natural history of diseases common in the elderly such as osteoporosis, diabetes, blindness, cancer, hypertension and atherosclerosis.

Several animal studies attempt to look at the various phenomena related to aging and nutritional parameters. Investigators have reported that some strains of rats and mice live considerably longer when their diets are restricted either by feeding them every other day, or by reducing their calorie and/or protein levels each day. Recent studies at NIA's Gerontology Research Center (GRC) indicate that diet restricted rats not only live longer but are also smarter and healthier than rodents allowed

to eat freely. For example, the older diet restricted rats learned complex mazes about as well as young rats, and much better than aged rats fed freely. Their kidney function was similar to that of young rats and much better than the freely fed older rats.

In terms of the effect of different schemes of dietary restriction on aging and longevity, it appears that a reduction of protein and calories is the most effective dietary scheme for prolonging life in rats. These data also suggest that food restriction begun in adult life is almost as effective in extending life as is life-long food restriction.

Caloric restriction alone retards bone growth and alters bone composition, i.e., bone is less dense, less well calcified, and has a higher lipid content. In addition, these rats do not have the normal age-related increase in calcitonin, the hormone that acts to inhibit bone resorption.

In order to more clearly understand the biological mechanisms by which caloric undernutrition retards immunologic aging and therefore extends lifespan the following five hypotheses are being studied in animals: possible shifts in lymphocyte subpopulations; effects on intrinsic age-related biochemical lesions in lymphocytes; slow down of age-related changes in thymic differentiation; changes in the micro environment with age; and amelioration of the autoimmunity of aging. Dietary restrictions are instituted at different periods of the lifespan (weaning, 12, 18, or 24 months) with particular emphasis on adult-initiated restriction. The diets are modified by varying protein levels over the lifespan, replacing sucrose with dextrose, adding retinoids, and balancing or restricting fat intake among groups differing in caloric intake. Psychological testing will be done to determine if undernutrition without malnutrition affects behavior, i.e., intelligence. Brain morphology, lifespan parameters, growth rates, body weight parameters, and disease frequencies with an emphasis on cancer and immune complex diseases will be determined. Methods to test the various hypotheses include enumeration and functional assays of B cells, T cell subsets, and determinations of cyclic AMP and GMP and their generating enzymes, energy change, adenosine deaminase and kinase 5'nucleotidase, nucleotide phosphorylase, catalase, mitochondrial respiration, DNA damage following UV and gamma injury, etc.

In an attempt to clearly define the various parameters with aging that are most conducive to a reduction in the risk of spontaneous tumors, studies in rats are investigating the hypothesis that dietary practices early in life moderate tumor susceptibility throughout an individual's lifetime. Results have shown that animals permitted to eat freely had a significantly shorter lifespan and more tumors over the same period of time than the experimental group of rats on specific diets. An animal model used to describe the conditions that contribute to the susceptibility of spontaneous tumors of the anterior pituitary gland has shown an unusually high growth rate associated with a high level of the food consumed and converted into body mass during early life, and a high intake of protein relative to body weight during early life. The emphasis of much of this research is on the dietary influences in the aging immune apparatus with special interest on immunologic suppressor effects, as well as on the efficacy of adult onset dietary restriction as an inhibitor of spontaneous carcinogenesis.

Other studies in animals are testing the hypothesis that subeffective brain damage (or effective damage) in younger adult rats yields symptoms of catecholamine deficiency during old age. The question of whether special feeding regimens can reduce or prevent catecholamine deficiency is being investigated.

The development of atherosclerosis, coronary heart disease, stroke, hypertension and blindness with age are common concerns in geriatrics research. One study on the effects of a fish oil diet on the natural history of coronary and cerebral atherosclerosis in monkeys has provided strong evidence that the atherosclerosis sparing effect of the fish oil is due to the preferential incorporation of that fatty acid into the platelet membrane phospholipids, which changes platelet function in ways favorable to diminishing atherosclerosis.

Accumulation of fluorescent pigmented material, lipofuscin, in the retina is a usual consequence of aging. Lipofuscin is thought to originate from the oxidation of cell products such as unsaturated lipids, including polyunsaturated fatty acids and vitamin A. Studies in rats indicate that high dietary levels of vitamin A greatly increase the rate of accumulation of lipofuscin in the retinal pigment epithelium, and that this phenomena is further exacerbated when vitamin E is limited. The level of vitamin E as a natural antioxidant may impede the rate of oxidation in ocular tissue and hence influence the rate at which lipofuscin accumulates.

Studies of glucose intolerance and diabetes in elderly subjects have shown that basal glucose production is approximately 10 percent less than that in young adults. Glucose carbon recycling and glucose oxidation estimated from $^{13}\text{CO}_2$ excretion, however, did not differ significantly between the two age groups when expressed as a percent of glucose production. Furthermore, elderly adults were capable of suppressing hepatic glucose output to the same degree as young adult controls when infused with various concentrations of exogenous glucose. These studies demonstrate that reduced glucose tolerance seen in the elderly is due to an impairment in the sensitivity of peripheral tissues to glucose uptake.

In terms of changes in the digestion and absorption of nutrients with age, the changes in the bacterial flora in aging individuals has been shown to decrease the resistance to pathogenic microorganisms which results in a decreased absorption of essential nutrients leading to malnutrition. This process has been reversed by antibiotic treatment.

Nutrition Education for Professionals

Nutrition education activities for the various health professionals, i.e., physicians, research scientists, nutritionists, registered dieticians, nurses and other support staff, are critical to the advancement of nutrition sciences. The adequate dissemination of new research findings is important to practical applications in the field. NCI and NHLBI have specific mandates for providing education programs to the professionals, while NIADDK, DRR, NIA, and NICHD also supported nutrition education activities for professionals.

The mechanisms used by the NIH to provide nutrition research information to the professional include publications in various medical and scientific journals such as the Journal of the American Medical Association, American Journal of Clinical Nutrition, Journal of Pediatrics, Journal of the National Cancer Institute, Journal of Clinical Investigation, New England Journal of Medicine, Journal of the American Dietetic Association, and many others. For example, the November 1982 supplement to the American Journal of Clinical Nutrition, volume 36, number 5, contained the proceedings of the symposium, "Evidence Relating Selected Vitamins and Minerals to Health and Disease in the Elderly Population in the United States," held in May 1982.

Other nutrition publications published primarily for professionals by various NIH Institutes as well as the NCC office include: three publications, "Obesity: Does it Modulate Infectious Disease and Immunity," "Overview of Nutritional Status in the United States," and "National Nutrition Policy in the United States" that appeared in Nutrition in the 1980s, Constraints on Our Knowledge (Alan R. Liss, Inc., New York); two publications, "A Model Workshop for Nutrition Counseling for the Reduction of Cardiovascular Risk Factors," and "A Manual in Nutrition Counseling for the Prevention of Coronary Heart Disease," prepared jointly by NHLBI and the American Heart Association, are intended to enhance the interviewing and counseling skills of the nutrition counselor. In addition, the tenth revision of the Recommended Dietary Allowances (RDA's) and a manual entitled How To Use The RDA's are being prepared through a contract with the Food and Nutrition Board, National Research Council (NRC) of the National Academy of Sciences (NAS).

An important mechanism for imparting nutrition information to the professional is through various workshops and conferences. In FY 1982, 13 conferences were sponsored by NCI, NHLBI, NIADDK, NICHD, NIA, NIAID, NEI, FIC, and the NCC.

In addition, representatives from the Institutes are members and provide support to international groups such as the International Vitamin A Consultative Group (IVACG). This group, which is composed of policymakers, scientists, and representatives of funding government agencies, seeks to reduce blindness due to malnutrition through an increased awareness of the problem and various intervention programs. IVACG, with support from NEI, is preparing for publication a manual on Biochemical Methodology for the Assessment of Vitamin A Status and a companion volume of Reprints of Selected Methods for Analysis of Vitamin A and Carotenoids in Nutrition Surveys. The work of this group is aimed at the education of the professional in the control of blindness due to malnutrition.

The seven Clinical Nutrition Research Units (CNRU) have active educational programs for professionals in accordance with one of the three stated objectives of a CNRU: "To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition." For example, a new 10-hour elective course in nutrition is being offered to the second year class of medical students at the Cornell University Medical College with assistance from Memorial Sloan Kettering Cancer Hospital's CNRU team.

An important multi-institutional effort to assist and encourage education in clinical nutrition has led to the establishment of a "Regional Center for Education in Clinical Nutrition in the New York-New Jersey Metropolitan Area." This center serves as a resource, planning and evaluation agency for faculty in 10 medical schools, 5 dental schools, 2 schools of osteopathy and major teaching hospitals in the region. The center's staff, in cooperation with faculty members, obtains information on the current status of nutrition in the curriculum, on the availability and effectiveness of nutrition training programs in the clinical years, and on the quality of audiovisual and printed nutrition materials. They also have developed a "lecturers bank" for teaching purposes and work with the physicians and other health professionals in order to develop both comprehensive and specialized clinical electives in nutrition. Periodic surveys will determine changes in the extent, quality, and effectiveness of nutrition teaching programs.

International Nutrition Research

International nutrition research continues to be important in advancing nutrition science, in assisting in the solution of food and nutrition problems throughout the world, and in strengthening our international relationships. International nutrition research includes studies that utilize the special talents and different environments available in studies conducted in the less developed countries by U.S. or foreign scientists. Studies are also conducted by foreign scientists working in the U.S. or other countries of the developed world. In FY 1982, NICHD, NCI, NHLBI, NIADDK, NIEHS, NIAID, DRR, NEI, and FIC supported international nutrition research.

In the absence of a solution to the maldistribution of the world's food supply, research on common states of undernutrition, such as protein-calorie malnutrition, and iron and vitamin A deficiencies, attempts to determine how these states affect the growth, development and overall health status of individuals. Research also examines the individuality and adaptation processes of various populations under certain conditions in order to develop the appropriate nutritional support.

Undernutrition, superimposed on various disease states, particularly diarrheal infections which cause impaired utilization and loss of nutrients, is the primary cause of death of children under the age of 5. One study of protein/calorie malnutrition (PCM) in children, under way in Guatemala, is examining serum factors responsible for the opsonization of bacteria. Deficiency of complement and of complement-mediated opsonins, known to occur in malnourished hosts, may play a role in the high incidence of fatal gram-negative septicemia in acute malnutrition. The effect of dietary therapy alone or dietary therapy plus replacement of complement in the form of fresh-frozen AB/Rh+ plasma on serum complement levels and opsonin activity is being assessed in these children with PCM. Results from the study indicate that dietary therapy with the replacement of complement in the form of fresh-frozen plasma increases functional complement activity in the serum of undernourished children. This plasma has also been shown effective in increasing complement activity in chronically ill adults suffering from protein calorie malnutrition in developed countries.

Another study of deficiency states in preschool children is under way to assess whether a low dietary intake of zinc contributes to poor linear growth velocity. Preschool children of Mexican-American ethnic origin were given a 10 mg/day supplement of dietary zinc; only children in the lowest 10 percent height for weight were included in the study. Only boys appeared to have a significant increase in linear growth velocity with the supplement.

Research on zinc deficiency in young men revealed that RNAase activity is significantly increased in the parotid saliva and blood plasma during zinc depletion, and returns to normal with zinc repletion. Leukopenia with relative lymphocytosis is also present in zinc deficient men, indicating that the effects of zinc on man's immune function also deserves attention.

Iron deficiency and iron deficiency anemia is another area for international investigation. Research on iron deficiency has shown an association between increased red blood cell membrane stiffness and decreased red blood cell survival in iron deficiency primarily due to decreased membrane viscoelasticity. Iron deficient red blood cells have an increased susceptibility to peroxidation and spontaneous crosslinking of membrane protein and lipid.

Studies on the effects of anemia versus tissue iron deficiency on work performance in rats employed exchange transfusions to control the hemoglobin concentration in both tissue iron deficient and control rats. Results from this work indicate that defects of $\dot{V}O_2$ max and aerobic work capacity result primarily from anemia, while endurance capacity depends on the capacity of muscle mitochondria to utilize oxygen and produce ATP.

The role of vitamin A status in blindness frequently associated with measles among children in developing countries is being investigated in India. Appropriate methods to assess vitamin A status are being tested in the field. Collaborative centers for research on cataracts and nutrition's role in their development are also planned for India.

One new test recently developed to assess vitamin A status of children as young as 4 years is a rapid dark adaptation test. The test involves matching the intensities of color disks to cone function (not rod function) so that under dim lighting conditions, the ability to separate the different colored disks depends on rod function alone. Some studies have shown that protein status affects the ability of the retina to utilize vitamin A. In patients with protein deficiencies, studies have shown that dark adaptation is uncorrectable with vitamin A or zinc alone. In such patients dark adaptation response did not improve until protein was repleted. A new approach to the assessment of vitamin A status seeks to identify and quantitate on a population basis the prevalence of subclinical vitamin A deficiency when biochemical and clinical signs are not present. Such an approach will provide a quantitative method for estimating the magnitude of the "at risk" population and the effectiveness of intervention programs to decrease the number of people "at risk" of developing clinical vitamin A deficiency.

In subjects with chronic hemolysis due to Mediaterranean type glucose-6-phosphate dehydrogenase deficiency, vitamin E supplementation appears to significantly increase hematocrit and hemoglobin levels, prolong red cell survival, and reduce reticulocyte counts. This finding was also apparent in a group of Israelis with glucose-6-phosphate deficiency.

Studies on the composition of breast milk and milk intolerances continue in order to increase our knowledge of the effects of infant feeding practices on subsequent development. The composition of breast milk from Mexican mothers is being compared with that from Houston mothers while taking into consideration differences in ethnic backgrounds, exposure to agricultural and industrial toxins, pathogens, and dietary intake. This study also includes a longitudinal eipdemiological study of breast-fed and bottle fed infants in order to evaluate the stability of protective factors of human milk with regard to refrigeration, freezing, and pasteurization. The possibility of passive protection (in breast-fed infants) from gastroenteritis due to enteropathogens will be examined. Results from this research will help to develop guidelines for banking and storage of human milk.

The prevalence of milk intolerance due to lactase deficiency in the Inuit Eskimos and Indians of Canada is shown to be approximately 73 and 60 percent, respectively. By ascertaining levels of vitamin D and its metabolites in Eskimo and Indian children, the investigators will relate the prevalence of milk intolerance among these groups to the effectiveness of the Canadian program of milk fortification with vitamin D.

Investigations in Costa Rica and Colombia are analyzing human fertility patterns in relation to the duration of breast feeding, as well as to proxies of nutritional status such as sharecropping and land tenure. Additional work on the relationship of subsistence patterns, dietary intake, and nutritional status of inhabitants, particularly children up to 5 years of age, is being carried out in the Sudest Island and the Louisiade Archipelago of Papua, New Guinea. Malnutrition in children has been reported to be approximately 96 percent in the Sudest Island; rates of malnutrition appear to follow cultural rather than environmental boundaries. Preliminary findings suggest that changes in the subsistence patterns on the island from a reliance on the collection of wild foods and fishing to a heavy emphasis on the cultivation of starchy root crops have had a deleterious effect on nutritional status. Also, traditional proscriptions against feeding young children any animal foods are strictly followed in some areas of hyperendemic malaria. These areas also report the highest rates of child malnutrition. Data suggest that the plasmodium do not live within the red blood cells of hosts with a marginal nutritional status, therefore, these malnourished children may be partially protected from the disease.

A study in Kenya is making attempts to quantitate the negative effects of Schistosoma hematobium infection on nutritional status and to evaluate the benefits of oral antischistosome drug treatment on nutritional status.

One of the main avenues through which NIH supports international nutrition research activities is the U.S.-Japan Cooperative Medical Sciences

Program and its Malnutrition Panel. Specific areas of research involve studies on the effects of changing dietary patterns on disease; the effects of malnutrition on lactation, reproduction, physical and mental development, and work performance; the interaction of nutrition, immune competence and infection; and the influence of environmental and host factors on nutritional requirements. Although the people in Asia remain the primary area of interest, research in other developing countries may be included under the auspices of the U.S.-Japan Cooperative Medical Science Program and its Malnutrition Panel.

Since the primary diseases afflict persons in both the developed and the lesser developed countries of the world, international nutrition research examines cancer incidence in various populations, the prevalence of lipid disorders and the effect of diet on these disorders, and the relationship of these disorders to cardiovascular disease.

A number of epidemiological studies examine the possible relationship of diet and/or nutritional status on the incidence and natural histories of cancer. One study in Colombia is investigating the prevalence of cancer with geographical pathological findings, while a number of interdisciplinary investigations are looking at the nutrition related risk factors for the major cancers in populations from Japan, Yugoslavia, Finland, and in many U.S. cities. The demographic and clinical features of an Albino population in Tanzania are being studied in terms of their possible relationship to the high incidence of skin cancers. A clinical trial on the use of 13-cis-retinoic acid on the chemoprevention of skin cancer in this population is also under way.

A number of studies are examining the carcinogenic risks of chemicals to humans. Two studies involve N-nitroso compounds; one under way in the United Kingdom is attempting to develop analytic methods to determine the N-nitroso compounds in various foodstuffs, while the other under way in Canada is investigating biochemical and morphological changes in the development of liver cancer induced by diethylnitrosamine, 2 acetylaminofluorene, dimethylnitrosamine, and other hepatic carcinogens.

International nutrition research to look at environmental contaminants includes investigations on adaptive metabolic responses in gastrointestinal and pulmonary tissues to environmental xenobiotics. The influences of polybrominated biphenyl, polychlorinated biphenyl, and polychlorinated naphthalenes on biotransformation rates are being studied, as is the relationship between induction and the tissue level of xenobiotics. Intestinal biotransformation regulation by dietary factors is being evaluated in in vitro models and isolated intestinal sacs.

In the area of cardiovascular disease, a number of studies are under way in Israel, Canada, Puerto Rico, the USSR, Yugoslavia and the People's Republic of China. A cooperative agreement with Japan allows for experimental studies on the dietary prevention of hypertensive and atherosclerotic diseases. Epidemiological studies under way in the Lipid Research Clinics (LRC) are designed to generate internationally comparable information on plasma lipids and lipoproteins, cardiovascular risk factors, and demographic and nutritional status that will allow a comparison of the heart disease problem.

Data from the LRC in Jerusalem indicate that in native born 17-year-old army inductees, plasma cholesterol levels differ according to the country of parental origin. The highest cholesterol levels are seen in those with parents from the West, while the lowest levels were in those with parents from North Africa and Asia. Total fat, saturated fat, and cholesterol intake correlated with the plasma cholesterol level. Such investigations provide important insights into the cardiovascular risk factor associations in diverse populations.

Also under investigation are the risk factors contributing to glucose intolerance; obesity, diabetes and adipose tissue development; genetic factors that contribute to obesity; inborn errors of carbohydrate metabolism; and the nutritional management of osteoporosis.

Nutrition Conferences Sponsored by NIH

Each year the NIH sponsors a number of conferences on a variety of nutrition topics that reflect the current interest of the Institutes in areas of program development for nutrition research and training. Such conferences also help to expedite transfer of nutrition technology to scientists and educators so as to assure the appropriate application of research in practice. Table IV lists the conferences held in FY 1980-1982.

TABLE IV
NIH Sponsored Nutrition Conferences, FY 1980-1982

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NCI	Oct. 23, 1979	Conference on Esophageal and Prostatic Cancer in Blacks and Whites
NICHD	Oct. 24-26, 1979	Nutrition of the Child: Maternal Nutritional Status and Fetal Outcome
NCI	Dec. 10-12, 1979	Workshop on Fat and Cancer
NCI	Jan. 10-11, 1980	Symposium on the Nutrition of the Cancer Patient
NIADDK NCI, NIA, NIDR, NIEHS, FIC	Feb. 20-22, 1980	Conference on Micronutrient Interactions: Vitamins, Minerals and Hazardous Elements
NCI	Mar. 3-6, 1980	Seminar on Gastrointestinal Cancer
NICHD	May 5-8, 1980	Food, Nutrition, and Evolution
NIADDK NIDR, FIC	May 13-16, 1980	Second International Symposium on Selenium in Biology and Medicine

(Table IV, continued)

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NIADDK	June 9, 1980	Steering Group to Plan for A Workshop on Methods for Characterizing Obesity
NIAID, FIC	June 16-17, 1980	A Discussion Group on Infections and Undernutrition
NIADDK NCI FIC	June 29- July 2, 1980	Conference on Vitamin B ₆ Methodology and Nutritional Status
NIADDK	July 29-30, 1980	Workshop on the Effect of Nutrition on Human Growth and Development and Later Life and Health: Global Priority Issues
NIADDK NCI, NIA NHLBI, NICHD DRR, FIC	Aug. 10-14, 1980	Western Hemisphere Nutrition Congress VI
NCI	Sept. 15-16, 1980	Workshop on Lipid Oxidation, Vitamin E, Selenium and Carcinogenesis
NHLBI	Oct. 7, 1980	Symposium on Current Nutrition Issues in Hypertension
NIGMS	Oct. 9-10, 1980	Second Conference on Supportive Therapy in Burn Care
NCI	Oct. 17, 1980	Effect of Diets on Animal Studies Related to Toxicology
NIADDK	Nov. 15-16, 1980	Conference on Metabolic and Clinical Implications of Branched Chain Amino and Keto Acids
NHLBI	Dec. 3-5, 1980	The U.S.-Italy Joint Symposium on Nutrition and Cardiovascular Disease
NCI	Dec. 11-12, 1980	Research Needs for Nutrition and the Pediatric Cancer Patient
NCI	Mar. 4-6, 1981	Molecular Interrelations of Nutrition and Cancer: Thirty-Fourth Annual Symposium on Fundamental Cancer Research
NHLBI	Mar. 9, 1981	Jerome Cornfield Memorial Symposium on Biostatistics and Epidemiology
NEI	Apr. 6-10, 1981	Meeting on Support of a Nutritional Blindness Center in Hyderabad, India

(Table IV, continued)

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NCI	Apr. 7, 1981	Diet and Breast Cancer Risk Working Session
NCI NHLBI	May 11-12, 1981	Workshop on Cholesterol and Non-Cardiovascular Disease Mortality
NIADDK	May 28-30, 1981	Workshop on Oral Retinoids in Dermatological Disease
NHLBI	June 7-9, 1981	Workshop on Hypertriglyceridemia: Mechanisms and Role in Atherosclerosis
NICHD	June 9-11, 1981	Determinants of Choice and Duration of Infant Feeding Practices
NCI	June 25-26, 1981	Chemoprevention Workshop of the Board of Scientific Counselors
NCI	June 29- July 3, 1981	VII International Symposium on Gnotobiology
NIADDK	July 21-31, 1981	Food and Nutrition Component of the Gordon Research Conference
NIADDK	Aug. 15, 1981	Workshop on Nutrition Research Needs in Asian Countries
NIADDK, FIC, and Other Sponsors	Aug. 16-21, 1981	XII International Congress on Nutrition
NIADDK	Aug. 23-27, 1981	Fifth International Conference on Proteins of Iron Storage and Transport
NICHD	Aug. 31- Sept. 9, 1981	Milk Banking Methodology
NCC	Sept. 16-18, 1981	Conference on the Assessment of Nutritional Status
NICHD	Sept. 16-18, 1981	Trace Element Regulation of Immunity and Infection
NIADDK	Oct. 9-10, 1981	Workshop on Guidelines for Research Methodologies for Use in Studies on Mineral Content of Human Tissues
NHLBI NIADDK FIC	Nov. 11-13, 1981	Conference on Vitamin E: Biochemical, Hematological and Clinical Aspects

(Table IV, continued)

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NEI	Nov. 16-17, 1981	Nutrition, Pharmacology and Vision
NIAID NICHD	Jan. 13-15, 1982	NIH Consensus Development Conference on Defined Diets and Childhood Hyperactivity
NCC	Jan. 25-26, 1982	Workshop on Body Weight, Health and Longevity
NIADDK	Feb. 14-19, 1982	Fifth Workshop on Vitamin D
NIADDK	Apr. 29-30, 1982	Nutritional Therapy in Chronic Renal Failure Conference
NIA	May 8, 1982	Assessment of the Evidence Relating Selected Vitamins and Minerals to Health and Disease in the Elderly Population in the United States
DRG	June 11, 1982	Workshop on Nutrition and Endocrine Disorders
FIC	June 21-25, 1982	1982 Gordon Research Conference: Lipid Metabolism
NIADDK	Aug. 9-12, 1982	1982 Gordon Research Conference: Food and Nutrition
NICHD	Aug. 30- Sept 2, 1982	Workshop on Breast Milk Banking: Current Status and Future Needs
FIC	Sept. 1-4, 1982	Third Congress on Nutrition and Metabolism in Renal Disease

The Videotape Series, "Eat Well, Be Well"

In FY 1981, the NCC was asked to serve as consultants to the production of a series of videotapes on various nutrition topics entitled "Eat Well, Be Well," produced by Amram Nowak Associates and funded by Metropolitan Life Insurance Company.

This first "Eat Well, Be Well" series consists of 26 four and one-quarter minute videotape segments and 1 thirty-minute anthology. Each segment presents in a practical and visually pleasing manner the scientific state of the art and rationale behind the many aspects of the DHHS/USDA joint publication, Nutrition and Your Health, Dietary Guidelines for Americans. The series features nutrition messages illustrated by recipe and menu suggestions.

On March 24, 1981, the entire series was beamed via satellite to the 225 Public Broadcasting System (PBS) television stations across the country. To date, a number of responses received by the NIH from station and program managers of the PBS stations have indicated their enthusiasm to include this well done series on nutrition as part of their regular programming schedules. The series has also been used as part of various station's in-school programming.

In August 1981, the NCC exhibited the first "Eat Well, Be Well" series at the XII International Congress of Nutrition held in San Diego, California. The exhibit, produced and manned by representatives from the Metropolitan Life Insurance Company, was visited by approximately 1,500 participants at the congress from around the world. Requests for copies of the series came from England, Australia, Canada, Africa, Mexico, and other countries. Representatives from industry, universities, and the media previewed and expressed an interest in the series.

In order to increase its marketability and promotion, the NCC has transformed the videotape series into 16 mm film that can be shown easily at schools, church organizations, clubs, etc. Plans for promoting the series include making it available, either as videotape or film, to the USDA Home Extension Service, the Society for Nutrition Education, and other interested agencies or organizations. Eight segments of the series are being shown continuously through a super 8 film cassette as part of a permanent free standing exhibit developed by the NCC and displayed in the new Ambulatory Care Research Facility at the NIH.

Due to the tremendous wide public and professional acceptance of the first "Eat Well, Be Well" series, the Metropolitan Life Foundation awarded a grant to Amram Nowak Associates for the production of the sequel, "Eat Well, Be Well II", also done in consultation with the NIH-NCC. The second series is an excellent example of joint collaboration among industry, government, and the scientific community in promoting nutrition and public health. It includes 14 7-minute videotape segments, 9 of which feature prominent physicians speaking on the role of nutrition in health promotion and disease prevention. Former DHHS Secretary Schweiker is featured in one segment on "Diet and Exercise." Again, appropriate recipes are demonstrated for each of the following topics covered in the sequel: vitamins and minerals; carbohydrates; prenatal diet; milk and dairy products (osteoporosis); dieting; protein (production of lean meat); body weight; alcohol; fiber; vegetarianism; food substitutions; ethnic foods; cholesterol; and exercise.

The second "Eat Well, Be Well" videotape series was beamed to all PBS stations by satellite early in July, 1983. In addition, plans are under way to include viewing of both "Eat Well, Be Well I and II" as part of the National Health Fair Program, coordinated by the National Health Screening Council for Volunteer Organizations, Inc. The series is most appropriate for nutrition instruction in primary and secondary schools, by church groups, as part of health fairs, and by any group interested in the role of nutrition in health and disease.

Alcohol, Drug Abuse, and Mental Health Administration

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) consists of the following three Institutes: National Institute of Mental Health (NIMH), National Institute of Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). ADAMHA supports limited research in human nutrition as part of its mission to develop knowledge to assist the nation in understanding and addressing mental illness and the abuse of alcohol.

In FY 1981, ADAMHA for the first time joined with the NIH in publishing a joint PA in nutrition, "NIH New Investigator Research Award (NIRA) in Nutrition--ADAMHA Special Notification for Research on Nutrition and Behavior." NIMH and NIAAA joined NIH in encouraging new investigators to develop their research interests and capabilities in various aspects of nutrition and behavior. This joint program announcement is described on page 31.

In general, ADAMHA supports extramural and intramural research to assess biological and behavioral factors related to such eating disorders as obesity, anorexia nervosa, and uncontrollable excessive eating, known as bulimia. It also supports research on the relationship of drug abuse and nutritional status, the relationship of nutrition to brain development and function, the effects of malnutrition on the development of cognitive processes, the effects of various nutrients (such as sucrose) on hyperactivity in children, as well as the problems of secondary malnutrition in alcoholics and the mechanism of the fetal alcohol syndrome. These various areas of nutrition research are described below by funding Institute.

National Institute of Mental Health

The National Institute of Mental Health (NIMH) supports intramural and extramural nutrition research. Investigations conducted by NIMH consider the relationship of nutritional status to mental health, with studies under way on cognitive and emotional development as a function of chronic malnutrition and undernutrition. The biological, behavioral, and/or psychological factors related to the development of obesity and anorexia nervosa are being examined, as well as the cognitive, emotional, motivational and psychosocial factors that may be predictive of these nutrition related behaviors. Other studies focus on the relationship of nutrition to normal and abnormal brain development, on nutrient imbalances in persons with mental disorders, and on possible food allergies that may produce symptoms or behavior typical of mental disorders.

In FY 1982, the NIMH extramural research program in nutrition supported 40 research grants, that include career awards, regular research grants and small grants for a total of \$1.9 million. The areas of research interest ranged from human studies on obesity, anorexia nervosa, bulimia, nutritional status of psychiatric patients on various psychotherapeutic drugs and treatments, to basic research on the effects of psychotherapeutic drugs on feeding behaviors in animals and the possible neurochemical mechanisms of such behaviors. Other studies focus on the use of lecithin in the treatment of tardive dyskinesia and in Alzheimer's disease.

Anorexia nervosa, a disorder characterized by self-imposed starvation, amenorrhea, depression, and mood changes, is one primary area of research interest. Results from a collaborative study which provided anorexia patients with either pharmacological or behavioral treatment have shown that the patients were mild to moderately depressed, that the depression decreased with treatment, and that weight gain correlated with the decrease in depression. A 10-year followup study of these patients has been initiated. Two additional studies on anorexia nervosa focus on the endocrinological and psychological disturbances, and the psychopathology of the disorder.

Nutrition research under way as part of the NIMH intramural program includes studies on the effects of caffeine and sugar in children, the effects of malnutrition on cognitive development in the young, and the psychological effects of the chloride deficient soy formula on infants. The FY 1982 support for this research totaled \$28,000.

An interesting workshop on "Nutritional and Dietary Interactions in Preventive Mental Health," was sponsored by the Prevention Research Branch of NIMH. This workshop focused on two areas of interest among mental health researchers and service providers: 1) the potential that proper nutrition and other lifestyle practices have for preventing emotional and cognitive disorders; and 2) the usefulness of nutrition support strategies in treating such disorders.

The scientists attending the workshop represented a variety of disciplines from epidemiologists to neuroanatomists. During the first day, they examined the effects of maternal malnutrition on prenatal and post-natal development, and noted that while animal research has demonstrated a clear link between a mother's nutrition and her offspring's brain development, these findings have yet to be applied in creating appropriate preventive strategies for humans. Two areas noted worthy of further study, due to their particular significance for the developing nations and potentially integral role in reversing America's cycle of poverty, include the role of specific nutrients in the development of specific brain structures, and the possible reversibility of nutritional deficits during pregnancy.

The research presented on the second day highlighted the possible link between food substances and behaviors due to the national interest in the effects of food additives, vitamins, and diet on behaviors and emotions. The concept "cerebral allergies," a term used to describe emotional/cognitive reactions independent of physical reactions to food substances was debated. Researchers agreed that further investigations of these allergies are needed and that innovative research designs will be required to identify that small but significant group of individuals who very much are "what they eat."

In the workshop's summary session the importance of lifestyle variables, including dietary practices, in relation to the ten leading causes of death was emphasized with direct links based on scientific and clinical data made between an individual's behavior and probable quality and length of his or her life. One of the significant issues suggested

for prevention researchers through the 1990's was "how to get people to accept and make use of what we learn."

National Institute on Drug Abuse

The National Institute on Drug Abuse (NIDA) supports studies on the effects of nutritional status on maternal narcotic addiction and child development, drug abuse and perinatal brain development, as well as the effect of maternal drug abuse on the nutritional status of the offspring.

National Institute on Alcohol Abuse and Alcoholism

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) research program in nutrition primarily addresses the detrimental factors of alcohol abuse as they relate to human nutrition. Studies focus on the effects of alcohol on the structure and functions of the gastrointestinal system, i.e. digestion, absorption, and transport of nutrients. A significant part of this research deals with the ethanol-induced alterations of mineral and vitamin metabolism as well as changes in protein and amino acid metabolism. The influence of nutritional status on alcohol metabolism is also being investigated.

In addition, studies are under way on the fetal alcohol syndrome with investigations to consider the effect of alcohol on the nutritional status of the pregnant woman and consequently on the developing fetus, the effect of maternal drinking on the transport of nutrients across the placenta, and the role of alcohol in the maternal nursing of the newborn. In FY 1982, NIAAA's support for 6 extramural nutrition research projects totalled \$622,000.

Health Resources and Services Administration

The Health Resources and Services Administration (HRSA) is responsible for health service delivery programs and manpower development programs which have nutrition components. The three bureaus of HRSA that support nutrition research activities are the Bureau of Health Care Delivery and Assistance, the Indian Health Service, and the Bureau of Health Professions.

Bureau of Health Care Delivery and Assistance

The Bureau of Health Care Delivery and Assistance serves as a national focus for providing primary health care services, preventive health services, specialized health care and the redistribution of health care professionals to health manpower shortage areas in order to promote the availability and accessibility of services to persons who are without a regular source of services.

Nutrition research supported by the Bureau of Health Care Delivery and Assistance falls under the auspices of the Division of Maternal and Child Health. The investigator-initiated research projects that respond to the needs of mothers and children include studies on nutritional abuses and pregnancy outcome, maternal phenylketonuria and hyperphenylalaninemia, and trace metal interactions in children exposed to lead. Responsibilities in nutrition research include stimulating and supporting studies in nutrition which will improve the delivery of health care to mothers and children, disseminating and interpreting the findings from these studies, and helping health care programs to utilize them.

In addition, research is conducted as an integral part of HRSA-supported training projects. These projects include those related to perinatal/neonatal nutrition, mental retardation, and adolescent health funded under the Maternal and Child Services Block Grant Program.

Indian Health Service

Nutrition research supported by the Indian Health Service includes studies on native Americans and Alaska natives that focus on the incidence of obesity on the Warm Springs Indian Reservation, and studies of Navajo women during and after pregnancy.

Bureau of Health Professions

The Bureau of Health Professions supports special projects and traineeships that apply nutritional science to health care practices. The nutrition research studies supported by the Bureau include studies on prolactin response to suckling and milk yield in women at risk for poor lactation, and on the effects of maternal dietary intake on the bilirubin levels of breast-fed infants.

Centers for Disease Control

The Centers for Disease Control (CDC) conducts both domestic and international nutrition activities aimed primarily at the evaluation of nutritional status in order to provide necessary information for nutrition-related decisions in health programs. The Division of Nutrition, located in the Center for Health Promotion and Education, is the focal point for coordinating nutritional status surveillance activities conducted by the States and for carrying out selected nutrition survey assessment activities within the United States and abroad. The CDC surveillance and survey activities provide information to the State and local level that complements the National Center for Health Statistics' data concerning the overall nutritional status of the total U.S. population. Intramural applied research activities focus on the development of nutritional status assessment guidelines, uniform procedures, and evaluative criteria.

One major thrust of nutrition activities at CDC involves the work of the Division of Nutrition with selected State and local health departments in developing a national nutritional status surveillance system. In FY 1982, 32 States encompassing 2,200 service delivery clinics furnished data on the nutritional status of approximately 1 million annual screening and follow-up visits. The surveillance system is designed to monitor continuously the status of major nutritional problems in the United States. It is based on information collected routinely in service delivery programs, such as the Maternal and Child Health programs, the Women, Infants and Children feeding programs, etc. This information includes measurements of height, weight, hemoglobin, and/or hematocrit levels, and is analyzed and compared with a reference population in order to characterize the nutritional status of the study population. The analysis is returned to the service delivery source for immediate use in program planning, management, and evaluation of health resources at the State and local level. These surveillance activities concentrate on low income populations at risk for nutritional problems and are a major source of data on the nutritional status of the American people. In addition, 18 States have nutritional surveillance systems for pregnant women in order to monitor the prevalence of common nutrition-related problems in high-risk prenatal populations.

Technical assistance and consultation are also provided to selected States on the overall management of Health Education Risk Reduction programs that have a nutrition component. This assistance includes the areas of problem definition, setting of program objectives, defining strategy options, and program evaluation. Currently, major emphasis is placed on assisting States to undertake rapid, low cost telephone surveys to determine the prevalence of behavioral risks and health-related problems associated with the leading causes of death and disability.

CDC conducts research to develop improved methods for nutritional status assessment and surveillance and to define the relationships of nutritional factors to a variety of adverse health outcomes, such as the effects of infant feeding practices on the incidence of infectious disease and growth retardation.

CDC collaborates with the National Center for Health Statistics (NCHS), which conducts the ongoing monitoring of national samples of the U.S. population through the National Health and Nutrition Examination Survey (NHANES), by providing central laboratory services to these surveys and conducting an ongoing program of development to upgrade the sensitivity and specificity of laboratory techniques used to assess nutritional status. The program attempts to improve technology and provide for a transfer of technology to other laboratories. The NCHS-NHANES survey and the CDC surveillance mechanism are complementary, with each one important for the development and management of programs needed to help eliminate nutritional problems.

In FY 1982, the development of laboratory methods that include new or improved methods for examining trace elements and vitamins was completed in order to support the NCHS Hispanic Study, an expanded follow-up of the NHANES II Study. This study, initiated in June 1982, uses the developed laboratory capability to perform biochemical analyses for 10 nutrients on approximately 8,000 study subjects.

Nutritional status assessment surveys are also conducted in selected less developed countries in collaboration with the Agency for International Development (AID) and other international agencies. These countries are provided with assistance in developing and evaluating mechanisms to monitor nutritional status of their specific populations.

Food and Drug Administration

Human nutrition research conducted by the Food and Drug Administration (FDA) is to provide information for safeguarding the nutritional quality of the nation's food supply and fostering the application of modern nutrition principles to the nutritional management of disease and injury. Other objectives include improving the consumer's understanding of food values and enhancing their perceptions of the importance of nutrition and health.

The intramural research program includes studies on: nutrient efficacy and safety that determine the necessary ranges of levels of nutrients and nutritional adjuncts needed to meet human needs imposed by a variety of environmental conditions; nutrient interrelationships in terms of disease prevention, e.g., the relationship between protein diets and the development of zinc deficiency symptoms; nutrient bioavailability for food and fortification purposes, i.e., to provide information for setting standards of quality for foods regulated by FDA; medical food assessments in order to determine the effectiveness with which such foods aid in the dietary management of disease conditions and to establish specifications for such foods; food composition and nutrient analysis in order to obtain information necessary for evaluating nutrition information used in labeling, assessing changes in the nutrient quality of the food supply, establishing fortification policy, and in general, enforcing compliance with the Food, Drug and Cosmetic Act; assessment of food and food constituent consumption levels in order to estimate the adequacy and safety of the nutrient intake by target subpopulations in the U.S.; and on consumer perceptions about food values and the nutritional quality of the food supply.

For over a decade the FDA has conducted an annual survey, the Total Diet Survey, that is designed to determine the levels of certain organic contaminants, heavy metals, and essential minerals. One component of the study, known as the Selected Minerals in Foods Survey (SMIF), monitors 11 essential minerals, including sodium, calcium, and iron. In FY 1982, the Total Diet Study was redesigned to allow for the study of yearly trends in the mineral (and heavy metal and contaminant) content of 234 individual foods representative of the American diet; daily intake and adequacy of the 11 minerals for eight age-sex groups; yearly mineral intake trends for each age-sex group; and the major food sources of the minerals for each age-sex group.

To increase the emphasis on nutrition research, the FDA issued 16 Requests for Proposals (RFPs) in FY 1980-1982. Those RFPs are listed in Table V.

TABLE V
Requests for Proposals in Nutrition Issued by FDA,
FY 1980-1982

<u>NUMBER</u>	<u>TITLE</u>	<u>APPROXIMATE DATE OF ISSUE</u>
223-80-2093	Design of Food Package Information Formats	Apr. 1980
223-80-2276	Comparative Study on Iron Status in Anemic School Aged Children	Jan. 1980
223-80-2282	Multi-purpose Survey	Mar. 1980
223-80-2298	Model System for Screening Food Additives for Spontaneous Activity in Rats	June 1980
223-80-2337	Product and Label Surveillance	Feb. 1980
223-80-2338	Quick Turnaround Survey Research Services	July 1980
223-80-2370	Development of Plaque Acidity Method for Evaluation of Cariogenic Potential of Foods	July 1980
223-80-2377	Food Consumption Data Bank	Apr. 1980
223-81-2395	Economic Cost Benefit Studies	Apr. 1981
223-81-2396	Economic Cost Benefit Studies	Apr. 1981
223-81-2397	Economic Cost Benefit Studies	Apr. 1981
223-81-2398	Economic Cost Benefit Studies	Apr. 1981
223-81-2399	Economic Cost Benefit Studies	Apr. 1981
223-82-2337	Product and Label Surveillance	Dec. 1981
223-82-2026	Food Label and Package Survey (FLAPS 83 Mini Survey)	July 1982
223-82-2393	Review and Evaluation of Key Pediatric Problems	Jan. 1982

In addition, through the Division of Consumer Studies, data is being obtained from the consumer public through surveys, and from the retail market place in the form of sales volume. The area of nutrition and consumer studies includes assessment of consumer knowledge, the measurement of the consumer's perceived needs for information, and the development of model education and information systems. In order to obtain information on the communication effectiveness of the food label, research on the eye camera (a precision measuring device for determining where on various parts of the food label the eye is focusing) attempts to assess the design of various nutrition labeling formats.

The 1982 Consumer Food Survey was conducted in conjunction with the NHLBI of NIH to establish a baseline of consumer knowledge, attitudes, and behaviors related to sodium consumption and hypertension. This survey included a national probability sample of 4,000 adults interviewed by telephone to assess consumer awareness and knowledge of the relationships between diet and health; e.g. sodium and hypertension, fats and cholesterol and cardiovascular disease, nutrition labeling information about salt and the sodium content of foods, etc. The first of a series of reports on these data, "The Public Response to Labeling of the Sodium Content of Foods," reveals that the number of people claiming to use label information to limit sodium consumption has increased from 14 percent in 1978 to 40 percent in 1982.

Another telephone survey, the vitamin and mineral survey, conducted in 1981, attempted to have respondents report vitamin usage on a brand name basis. The questionnaire covered circumstantial information of direct and indirect relevance to supplement use, such as sources of influence, whether taken under a physician's care, general dietary practices, snacking habits, vegetarianism, height and weight, a self-assessment of current state of health, and perception of degree of personal control over health. This survey is to be reported every 2 or 3 years in order to help track the anticipated growth in usage of vitamin and mineral supplements.

In market research, the Food Label and Package Survey (FLAPS) is an attempt to keep FDA informed about changes in the market place, i.e., changes of nutrition information, quantitative sodium labeling, and ingredient listing of food items. The sample consists of 1,700 food brands and is representative of packaged processed foods sold in grocery stores throughout the U.S. From the FLAPS III survey, completed in 1982, it appears that 19 percent of the packaged food sales now have quantitative sodium information.

UNITED STATES DEPARTMENT OF AGRICULTURE (USDA)

The Food and Agriculture Act of 1977 (P.L. 95-113) established USDA as the lead agency in the Federal government for the food and agricultural sciences, and directed that research concerning food and human nutrition be established as a separate and distinct mission of the Department. The USDA is authorized by legislation to provide the leadership, oversight and management necessary to assure that the Nation is provided with adequate supplies of high-quality food and fiber. To accomplish this, the Department supports and conducts a wide range of research, development, extension, and education activities. A major responsibility for assuring that national food and agricultural research needs are being met rests with the Department of Agriculture's research arm--the Agricultural Research Service.

Agricultural Research Service (ARS)

The mission of the ARS is to plan, develop and implement research that is designed to produce the new knowledge and technologies required to maintain the continuing vitality of the Nation's food and agriculture enterprise. As a Federal research agency, ARS (1) addresses problems that are of legitimate national concern, (2) conducts research that is appropriate for the Federal government, and (3) exploits the unique capabilities of ARS scientists and the facilities they operate--a combination that forms an integrated and coordinated national resource that is not duplicated by others in the full U.S. agricultural research and development system.

One of the major objectives that contribute to the goal of the ARS program is to develop the means for promoting optimum human health and well-being through improved nutrition. The American diet is undergoing rapid change; the ever growing variety of agricultural products, as well as the new processed foods that are being produced at increasing rates, are major contributing factors. The potential impact of these changes on human nutrition must be anticipated if the quality of the U.S. food supply is to be maintained. If the Nation is to keep pace with the growing need for food, it is essential that the nutritional quality of our food supply does not deteriorate. This requires knowledge that can only be derived from interdisciplinary efforts, interfacing nutrition research with pre- and post-harvest agricultural science and technology.

The ARS program is concerned mainly with understanding the relationship between diet and health maintenance. The major components of the ARS research program include emphasis on:

- ° Infant and child populations to determine nutrient needs for optimal growth and development, and on pregnant and nursing women to determine nutrient needs and requirements for themselves and their children.
- ° Adult populations to determine the biological functions of, requirements for, and interactions among essential nutrients and other dietary components.

- ° Aging populations to determine nutrient needs, influences of nutrient intake on changes in metabolism and functions of body systems of aged persons, and on the process of aging per se.
- ° Methodology development to support dietary intake surveys, nutritional status monitoring programs, nutrition intervention and other action programs.

To carry out its objective, ARS maintains five research centers around the country. These research centers focus on major components of the overall program. Scientists at the centers study a broad range of nutritional problems, and in the process develop innovative methods that benefit scientists in many other fields. They study nutrition questions from the viewpoint of a variety of disciplines and scientific perspectives; i.e., from research to education, and from biochemistry to analyses of food plans. Even though these scientists have individual areas of expertise, they work together to solve problems of common interest.

A description of the nutrition research under way at each of the five centers is presented below:

The Beltsville Human Nutrition Research Center (BHNRC) conducts basic and applied research to more completely define human requirements for essential nutrients, and identify through nutrient composition research those foods that meet the nutritional requirements. This research includes the determination of requirements for known nutrients, the search for yet unidentified essential dietary factors, the definition of the biological availability of nutrients and the study of interactions among them.

Scientists continue to investigate the metabolic effects of specific dietary constituents, such as sucrose and fiber; the optimum intake of nutrients to maintain health and minimize the risk of disease or toxicity; and interactions among nutrients and other dietary components. Studies under way in both human subjects and animals attempt to define the requirements for protein, fats, carbohydrates, vitamins, and minerals, and identify the forms in which those nutrients are most useful in meeting human needs. An integral part of this research program includes the development of new and highly sophisticated analytical instruments and techniques for sampling and analyzing foods, and for determining the roles of, and the requirements for, various nutrients.

Five laboratories comprise the BHNRC: The carbohydrate nutrition laboratory that investigates the mechanisms responsible for the various metabolic effects of different kinds of carbohydrates, and the effects of various carbohydrates on nutrient bioavailability and on risk factors for disease in order to determine the requirements of humans for carbohydrates and energy; the lipid nutrition laboratory where studies are under way to define the metabolic effects of different kinds and amounts of dietary fats in order to determine the optimum intake of fat for humans. Different dietary fats are investigated in terms of their effects on the synthesis and metabolism of prostaglandins, blood pressure, blood lipid levels, and the physiochemistry of blood platelet membranes as well as their relationship to the requirements for vitamin E and biotin;

the protein nutrition laboratory where investigators attempt to determine human energy requirements, particularly in terms of how they are influenced by dietary factors such as protein and by energy expenditures, as well as to determine metabolic responses to proteins and minerals and their interactions. Studies are also under way to examine the composition of fermented milk products such as yogurt and to determine the effects that conditions of fermentation have on the nutrition value of the products; the vitamin and mineral nutrition laboratory has studies under way to determine the modes of action and requirements for specific vitamins and minerals, identify the chemical forms and biological availability of vitamins and minerals in foods consumed by humans, and develop advanced analytical instruments and techniques for assessing trace elements and vitamins that affect nutrition; the nutrient composition laboratory provides essential data on the nutrient content of foods as consumed in the United States by: (1) analyzing foods for their nutrient content and supplying the results of these nutrient content analyses to appropriate groups and agencies; (2) designing and developing either new or improved methods for the analysis of nutrients in foods by conducting appropriate research in chemistry, biochemistry, and biology; (3) developing and utilizing sound sampling techniques to ensure that samples are representative of the U.S. food supply; (4) planning, developing, and conducting appropriate research on the effect of food processing procedures, transportation, and marketing methods, as well as food preparation procedures in the home, institutions, and restaurants on the nutrient composition of our diets.

The Children's Nutrition Research Center (CNRC) operates through a cooperative agreement between ARS and Baylor College of Medicine. Its research program was developed in collaboration with Texas Children's Hospital, the National Institute of Child Health and Human Development (NICHD) of NIH, and Baylor. The program is carried out within the Section of Nutrition and Gastroenterology of the Department of Pediatrics at Baylor. The CNRC conducts research to determine the nutritional needs and nutritional status of the pregnant and lactating woman, as well as the child from conception through adolescence. This research emphasizes the development of new methods to investigate the nutrient requirements in infants and to study the relationship between nutrition and growth and development. The three research programs under way by scientists at the center who collaborate on multidisciplinary investigations include the lactation program, weaning program, and stable isotope program.

The mission of the lactation program is to determine the composition of human milk through all stages of lactation and to assess the functional significance of its components, to determine the nutrient needs and allowances of the mother as well as the infant, and to study the maternal-infant behaviors related to the lactation process.

Studies under way as part of the weaning program attempt to determine the foods that should be introduced into the infant's diet in order to supplement maternal milk or infant formulas, and to investigate the disorders of the gastrointestinal tract that occur as a consequence of inappropriate weaning.

The stable isotope program's mission is to develop, with stable isotopes, methods of measuring bioavailability, absorption (or malabsorption), transport, utilization, and excretion of nutrients in the populations studied in the weaning and lactation programs.

A pregnancy program is planned as the next major area of research to be carried out by the center in order to allow for an integrated approach to the study of nutritional needs of humans from conception to the end of the first year of life.

The Human Nutrition Research Center on Aging operates through a Cooperative Agreement between the USDA, Tufts University and the National Institute on Aging (NIA), NIH. The center conducts research to determine the ways in which diet and nutritional status influence the onset of aging and the course of maturing in the U.S. population. The research, organized into programs on nutrient metabolism, nutrient requirements, nutritional epidemiology, functional systems, and drug-nutrient interactions, focuses on the following three questions: Does nutrition influence the rate of bodily functions as people grow old?; Does nutrition influence the development of chronic disabilities and disorders associated with aging?; and What are the nutritional needs of the elderly?

The nutrient metabolism program investigates the role of nutrients in regulating various metabolic functions with aging and in the elderly, i.e., the regulation of protein metabolism in arterial smooth muscle, the effects of dietary factors on cell metabolism and functions that are sensitive to changes with age, the factors that contribute to folic acid malabsorption in the elderly, and alterations in the absorption, transport and metabolism of fats and carbohydrates with age.

The program on nutrient requirements includes studies to determine the nutritional needs of the elderly for maintaining health and body functions, while the nutritional epidemiological program includes studies on the nutritional status of adults at various ages in order to identify the relationships between nutritional status and patterns of health and body functions.

The functional systems program focuses on the study of individual body system functions with age and the effects of past and present nutritional factors on those functions. Studies investigate the interactions of vitamins, minerals and hormones in the age-related loss of bone; hepatic and gastrointestinal function in aging; age-associated changes in skin cells; the effects of age on vitamin A absorption and vision; etc.

The drug-nutrient interactions program focuses on the effects of medicinal drug treatments on the nutrient needs of elderly persons through studies on the effects of changes in body composition with age; on the deposition, clearance and clinical effects of drugs; the effects of selected drugs on vitamin absorption; and the effects of steroid hormones on protein metabolism.

The Grand Forks Human Nutrition Research Center was established after a report to Congress by the ARS in 1963 emphasized the need for a national

research program in human nutrition to identify human requirements and characterize factors that affect those requirements. The center developed cooperative research programs with scientists at the ARS Northern Region Research Center in Peoria, Illinois, the ARS Spring and Durum Wheat Quality Research Laboratory in Fargo, North Dakota, and with scientists at various universities including the University of Montana, the University of Oklahoma, Tulane University, Wright State University and the Massachusetts Institute of Technology. The center conducts research to determine human nutrient requirements, particularly for minerals, in terms of various factors that influence these requirements, i.e., age, sex, physiological state, and stress; the interactions of mineral nutrients with each other as well as other nutrients and non-nutrients; the physiological and biochemical consequences of mineral deficiencies; and the bioavailability of minerals from foods.

The center includes an animal model research program and a human volunteer research program. The animal model program includes research in animals to define nutrient requirements in terms of metabolic and physiological function; to assess nutrient interactions; and to assess the effects of deficiencies of specific trace elements on the reproductive, immune, nervous, cardiovascular, and endocrine systems and on the molecular biochemical function of cells. In addition, the interactions of essential elements with each other and with non-essential, often toxic, elements are assessed with particular attention paid to the relationship of toxic trace elements to metabolic functions that depend on essential elements. Dietary factors that influence intestinal absorption and retention of trace elements are also studied.

The program involving human volunteers includes research to determine the bioavailability of trace elements, and the interactions among trace elements as well as with other dietary nutrients and non-nutrients. For example, the dietary factors that influence the bioavailability of trace elements are defined by balance studies, and by use of stable and radioactive isotopic tracers. In addition, the effects of mild deficiencies or supplementation with trace elements on metabolic and physiological functions are assessed. These functions include exercise and neuropsychological performance, endocrine function, thermal regulation, metabolic rate, glucose utilization, lipid and protein metabolism, and body composition.

The Western Human Nutrition Research Center, established in 1980, conducts research on human nutrition requirements and focuses on developing reliable, efficient, and inexpensive methods for defining nutritional status and evaluating nutrition programs; identifying factors, forces, and trends that result in malnutrition; and in supporting the identified needs of action agencies and the Department of Defense. The research carried out at the Center is done in cooperation with the Western Regional Research Center in Albany, the University of California at Berkeley, the University of California Medical School at San Francisco, and the University of California at Davis.

The research program is carried out at four units: The Bioanalytical Research Unit focuses on the development of rapid, effective, and efficient

methods for assessing the nutritional status of large populations; the Nutritional Physiology Research Unit investigates human energy requirements and nutritional factors that influence physical performance, and develops new techniques and methods that are sensitive, accurate and practical for field studies of human nutrition in order to evaluate performance and body composition; the Nutritional Requirements Research Unit conducts research to determine human nutritional requirements, especially for vitamins, for various age groups and activities, and to investigate factors that result in suboptimal nutritional status; and the Nutritional Status Research Unit conducts research on the assessment of nutritional and dietary status, and on factors that result in malnutrition and influence nutritional status. Macronutrient-hormonal interactions are emphasized.

Human Nutrition Information Service (HNIS)

The HNIS, a new agency within USDA established in 1981, incorporates those units within USDA that conduct food consumption surveys and nutrition education research. The mission of HNIS is to improve professional and public understanding of the nutritional adequacy of diets and food supplies; to develop new knowledge needed to improve the nutritional quality of diets; and to collect and disseminate technical and educational materials on food and human nutrition.

The HNIS activities fall under the Consumer Nutrition Division and the Nutrition Guidance and Education Research Division that conduct the research, analysis, and technical assistance activities of HNIS, or the Food and Nutrition Information Service that is responsible for information collection and dissemination. These activities are described below.

The Consumer Nutrition Division (CND) conducts the Nationwide Food Consumption Survey (USDA's major contribution to the National Nutrition Monitoring System); maintains the Nutrient Data Bank; and conducts, analyzes and interprets food and nutrition research in order to respond to practical problems faced by the public educators and government agencies formulating national and international food programs. The three branches that conduct these activities include the Nutrient Data Research Branch, the Food Consumption Research Branch, and the Food and Diet Research Branch.

The Nutrient Data Research Branch (NDRB) provides to researchers and others, accurate, up-to-date and comprehensive information in readily usable form on the nutrient composition of all important foods. Intramural activities of the Branch focus on gathering and evaluating published and unpublished data, processing the data through a computer system, so as to provide representative values of each nutrient in each food on a nationwide, year-round basis, and publishing revised tables on the nutrient composition of foods in accordance with advances in analytical methodology, changes in food supply, and the introduction of new foods. Development of improved methodology for rapid and accurate analysis of food nutrients and the generation of needed data on nutrient composition of foods are accomplished through extramural support of research.

Knowledge of the nutrient composition of foods is essential to basic research on nutrient requirements, nutrient metabolism and interactions, as well as for the practical application of assessing dietary intake and developing guidelines, food plans, dietary advice, and nutrition education programs. In light of this application, the NDRB interfaces with the Food Consumption Research Branch and the Food and Diet Research Branch. It also serves as the reference source for nutrient data used in the data base for the Nationwide Food Consumption Survey.

The NDRB's current program includes the following objectives: revision of the Agriculture Handbook No. 8, "Composition of Foods...Raw, Processed, and Prepared"; continued development of the Nutrient Data Bank; development and maintenance of standardized nutrient data bases for computerized dietary assessment; planning, developing, and monitoring of extramural research that develops improved methods of nutrient analysis or generates nutrient data; cooperating with other agencies, food industry, etc., in planning and conducting studies on nutrient composition; and cooperating with other countries and international organizations in the development of nutrient composition information.

The Food Consumption Research Branch (FCRB) provides information on the measures and adequacy of current levels and changes in the food and nutrient content of the U.S. diet to a number of individuals working in the areas of agriculture, food and nutrition intervention, food quality and regulation, nutrition education, food processing and distribution, economics, health, and welfare. The primary function of the FCRB is to maintain and update the U.S. statistical series on nationwide food consumption. The periodic Nationwide Food Consumption Surveys (NFCS) generate this information, which along with the NHANES, constitute the National Nutritional Monitoring System (NNMS). Under the NNMS, the individual food intake phase of the NFCS will become a continuous longitudinal dietary intake survey and the household food consumption survey phase will be conducted periodically. The first coordinated NFCS-HANES survey is planned for FY 1987, with field tests to be held in FY 1983-85.

Activities of the FCRB that relate to group surveys include the development of improved survey methods; dissemination of research results via computer tapes, a series of statistical handbooks and special reports and evaluations; and the maintenance and updating of highly complex technical information support systems for both the household and dietary intake phases of the surveys. Studies are now under way or planned to examine current survey methods and procedures in terms of timeliness, cost-effectiveness, response burden, and comparability with NHANES and other national nutrition surveys of households and individuals. The collection of dietary intake data on a single time or longitudinal basis is being examined, while the technical food information support system will be evaluated in terms of benefits, costs, and operation of the overall NFCS system.

Studies that make use of the NFCS data are also under way; e.g., a study of portion sizes was carried out to provide regulatory agencies with current information for estimating food ingestion levels among different population subgroups.

A close working relationship exists between FCRB and the Food and Diet Research Branch (FDRB), which is the primary user of the FCRB data. The FDRB interprets the data into forms usable by nutrition education specialists, etc. A complete description of the FDRB activities is provided below.

The Food and Diet Research Branch conducts, analyzes, and interprets research on food and nutrition in order to respond to the public, educators, and government agencies involved in the formulation of national and international food programs. It cooperates with the FCRB in planning the Nationwide Food Consumption Survey in order that the data address priority problems and that duplication of data tabulation and analysis is avoided. Data from the 1977-78 NFCS is currently being used to meet the following national program objectives: update of the USDA family food plan; a study of the economics of size in household food expenditures and use; a study of the effect of the food stamp program on diets; a study of the effect of the national school lunch program; and a study of food consumption patterns, food habits, and food preferences in the U.S.

Other studies under way use NFCS data to: identify areas of need for guidance in food selection; assess the levels of absorbable iron in diets of children, teenage girls, and premenopausal women; determine the nutrient contribution made by enriched and fortified foods to the diet; determine the importance of convenience foods in diets; appraise in-depth the eating patterns and food and nutrient intakes of the elderly; identify systematically the "good" and "important" food sources of nutrients which frequently fall below the RDA; and estimate the amount of sugar and other caloric sweeteners, sodium, and cholesterol in diets of various populations.

The FDRB research activities that do not depend on nationwide survey data include providing annual estimates of the nutrient content of the per capita national food supply, developing guidelines in food selection and preparation procedures for homes and institutions, and developing guidelines for use in managing food money.

The Nutrition Guidance and Education Research Division (NGERD) conducts nutrition research to improve the effectiveness and efficiency of nutrition education programs and to develop improved and practical applications of human nutrition research into nutrition education and information programs.

The two objectives of the NGERD research missions are:

- ° conducting a nutrition education research program to increase knowledge of nutrition education needs of different population groups and to improve methods for educating the public about food, nutrition, and health.
- ° analyzing and interpreting food and nutrition research to develop nutrition guidance concepts and techniques.

Current nutrition education research studies are evaluating the usability of nutrition and food guidance materials by household food managers, assessing the consumer's need and use of information on the safety and nutritive value of food ingredients, developing a food guidance system, and evaluating the nutrition education course developed in conjunction with the American Red Cross. Data from studies on food consumption, food composition, and dietary standards and recommendations are analyzed and considered in view of results from nutrition education and communications research. This approach is important for the development of strategies to apply and disseminate new concepts pertaining to nutrition that conform to usual food habits and also incorporate new nutrition recommendations.

The development of appropriate nutrition guidance methods by the NGERD includes the analysis of data from the 1977-78 Nationwide Food Consumption Survey for common patterns of food use, the development of a food guidance development data base and its adaptation as a test in a computer network, and the analysis of data from the NHLBI's Lipid Research Clinics data base in cooperation with NHLBI scientists.

Cooperative State Research Service (CSRS)

The CSRS, in coordinating and administering Federal funds for the research conducted by the States in agriculture, forestry, and home economics, works directly with the State Agriculture Experimental Stations (SAES), forestry schools, land grant colleges of 1890, Tuskegee Institute, and colleges of veterinary medicine. It also works with many other State and Federal organizations involved in agricultural and forestry research.

The organization of CSRS includes the Plant and Animal Sciences group and the Natural Resources, Food, and Social Sciences group which includes human nutrition. The research specialists in each group deal primarily with research planning, coordination, evaluation, and justification. Although CSRS is the responsible agency for formula and grant fund allocations, the agency's science specialists are responsible for the financial mechanisms.

Federal formula funding programs are administered by CSRS to more than 100 State institutions eligible by statutory formula or by administratively determined formula approved by the Secretary of Agriculture. These funds help to maintain the basic and applied research programs of the State research units, and foster cooperation among State research units and between the State and their Federal research partners. About 60 percent of the publicly-supported agricultural and forestry research is conducted by State institutions that receive support from CSRS. Every State as well as the District of Columbia, Guam, the Virgin Islands, Puerto Rico, Micronesia, and American Samoa has at least one agricultural experimental station. Both basic and applied human nutrition research is conducted by these research units. Specific research programs of the SAES involve investigators from a single station as well as active cooperation with other stations, Federal and State agencies, and industry and foundations.

The coordination of cooperative State-Federal research is done by CSRS scientists who serve on many technical research committees of the four USDA regions (Northeast, South, North Central, and West), and on many work groups, task forces, and advisory committees. Such committees are part of a formal research planning system. In addition, the CSRS scientists coordinate the review of proposed formula-funded research and research in progress, conduct periodic site visits to cooperating institutions in order to review current and recently completed research progress, and assist the State research units to develop 5-year research programs.

Federal funds administered by CSRS for human nutrition research include:

- (a) Funds mandated by the Hatch Act to at least one experimental station in each State;
- (b) Monies provided for research support at 16 land-grant colleges of 1890 and Tuskegee Institute; and
- (c) Funds for a special grants program for basic and applied research at nonprofit institutions of higher education or nonprofit organizations on a competitive basis. High-priority research funded recently included studies designed to increase understanding of human nutrient requirements.

It should be noted that the payments to the States from funds appropriated under the Hatch Act were originally required to be matched by the States. Over the years SAES funding of research from State appropriations and other resources has increased steadily with Federal formula funds now comprising less than 20 percent of all SAES funds. The USDA, through CSRS, exerts significant leverage on agricultural research across the Nation while contributing only a small percentage of funds from Federal tax sources.

The concept of a regional research program was developed by the SAES Directors and is included in basic legislation which indicates that not less than 25 percent of each station's allocation under the Hatch Act must be spent on research that is part of an approved regional project. Regional research supported by Section 3(c)3 of the Hatch Act is a joint effort directed toward solving specific problems related to agriculture. This research focuses on a problem of concern to two or more States, and is planned and conducted as a concerted effort of participating scientists mutually responsible for accomplishing objectives.

In human nutrition research, two regional research projects are a 5-year project on the nutritional status of adolescent females and a study to compare the effects of modifying fat in the diet on lipid metabolism. The first study includes a nutritional status assessment of 1,000 black and 1,000 white females, age 12 to 16 years and living in eight southern States. The nutritional status and health of these adolescents will be examined in relation to socioeconomic factors, food habits, nutrition knowledge, physiological development, etc. The second project will compare, in human subjects, the effects of a dietary fat intake patterned

after the USDA 1977 Food Intake Survey with those seen with a dietary fat intake patterned after the Dietary Goals of the U.S. Animal models will also be used to determine the impact of the USDA 1977 and Dietary Goals diets on metabolic parameters. This regional project was recently initiated as a result of research accomplished under a previous study that included collaborative investigations of dietary influences on different aspects of lipid metabolism in human subjects of different sex and age groups, as well as basic studies on experimental animals of the mechanisms of lipid metabolism and their modification by diet.

A partial compilation of CSRS human nutrition and food sciences research programs for FY 1981 are presented with their Federal financial support in Table VI below.

TABLE VI
CSRS Research in Human Nutrition and Food Sciences,
FY 1981

<u>Title of Program</u>	<u>Total Number of Projects</u>	<u>Fractional Number of Projects</u>	<u>Federal Support (in millions of \$)</u>
Nutritional Status Assessment	119	97.2	1.6
Nutrient Requirements	176	119.5	1.7
Nutrient Composition/ Bioavailability	408	318.2	2.8
Nutrition Education Research	<u>35</u>	<u>24.5</u>	<u>0.3</u>
Totals	738	559.4	6.4

VETERANS ADMINISTRATION (VA)

The VA's primary responsibility is to care for those who have borne the battle and for the survivors of those who died. There are 174 VA Medical Centers of which 130 have substantial research programs usually under an Associate Chief of Staff for Research, aimed at improving the quality of health care for veterans by constantly improving diagnosis and therapy. The VA does not compartmentalize its research components into "This is nutrition--that is endocrinology--that is heart disease, etc.," but a 1982 review delineated substantial nutrition components in 50 of the 130 VA Medical Centers with research programs. Nutrition research at the VA is not centralized, however, in that it is not directed from the VA Central Office.

The VA Central Office has a Clinical Nutrition Advisory Group, now under the joint direction of Drs. Neil Otchin and Edwina McDonald, which supplies nutrition advice to the VA Medical Centers. At the September 1982 annual meeting of the group, a basic nutrition evaluation was delineated as desirable for each patient entering every VA Medical Center.

Among the 50 nutrition research units within the VA system, studies range across every facet of nutrition--vitamins, minerals, hormones, carbohydrates, fats, proteins and water. Extensive research is under way on electrolyte balance, and total enteral and parenteral nutrition. These investigators are funded from both from the VA Central Office and from outside agencies; many are affiliated with medical schools and seek funding through the medical schools, which then request funds from NIH and various private foundations. Some VA nutrition research is supported, for example, by funds from the American Cancer Society, the Arthritis Foundation, the American Heart Association, the American Diabetes Association, the National Dairy Council, and other outside philanthropic agencies that support nutrition research related to their interests.

The full-time equivalent of approximately 300 M.D.s, and Ph.D.s, plus 600 support personnel (research technicians, registered dietitians, nurses, secretaries, etc.), are engaged in VA nutrition research. Many are "WOC" personnel ("without [VA] compensation"), spending 1 to 3 years under the direction of outstanding VA researchers at various VA Medical Centers, as visitors from academic institutions in the U.S. and abroad. Some of the WOC personnel are unpaid volunteers, but may receive salaries paid by affiliated medical schools, the NIH, the World Health Organization, the International Atomic Energy Agency, and many other organizations. The VA provides some of them with meals and occasionally housing, but no other funding. They add to the quality of the VA patient care at minimal cost to the VA.

Investigators involved in nutrition research in the field work in areas that have both immediate and long-term benefits in improving the quality of veteran patient care, and keep the VA in the forefront of applying the latest results of nutrition research to the day-to-day care of veteran patients.

The VA Research and Development Program has been reviewed by Marguerite Hays (Clin. Res. 31:28-30, 1983), with comments by a group of VA physicians (Clin. Res. 31:31-33, 1983). Space does not permit even a cursory review of the current activities at each of the 50 VA nutrition research units. Highlights of recent research results from eight of these units are given below.

1. Dr. Ananda Prasad's laboratory at the VA Medical Center in Detroit, Michigan, has been carrying out studies of zinc metabolism in animals and humans and has been generating important information for two decades. This laboratory has been engaged in defining marginal zinc deficiency. A pure zinc deficiency of marginal degree is induced in human volunteers by dietary means, and various zinc-dependent parameters are measured throughout the baseline, zinc depletion, and zinc repletion phases. Many biochemical parameters are being assessed which may eventually define marginal zinc deficiency. For example, over 100 enzymes are now known to require zinc for their functions. Studies have shown that some zinc-dependent enzymes are affected adversely in zinc deficient tissues of experimental animals, suggesting that the major role of zinc is probably enzymatic in nature. Deoxythymidine kinase has also been shown to be a zinc-dependent enzyme and that its activity decreases very rapidly in newly synthesizing collagen connective tissue, once experimental animals were made zinc deficient. This was accompanied by a decrease in DNA and protein synthesis.

Studies have particularly focused on the role of zinc in testicular function. In animal and human models, it has been established that the adverse effect of zinc deficiency is on the end organ, namely the testis, and that the pituitary-hypothalamic axis remains intact. Further studies are being conducted in experimental animals, in order to understand the mechanism by which zinc may affect testicular functions.

Recently studies have shown that zinc plays an important role in cell-mediated immunity; the thymus decreases in size as a result of zinc depletion. Many functions of thymic-dependent cells (T-cells) are affected adversely by zinc deficiency. The role of zinc on natural killer cells and Interleukin I and II is currently under investigation. Effects of zinc deficiency on nucleoside phosphorylase, an enzyme considered to be important for T-cell function, and the zinc concentration in lymphocytes are being assessed.

2. Dr. Herta Spencer's facility at the Hines VA Medical Center in Illinois is a 10-bed metabolic research unit fully occupied throughout the year. Studies are carried out under strictly controlled conditions; diets are prepared in the kitchen of the metabolic ward and all excreta is collected. The patients are supervised 24 hours a day by a nursing staff highly experienced in metabolic research. All analyses of the diet and biological samples are carried out in the laboratories of the metabolic unit.

The unit is conducting studies of mineral and trace element metabolism in humans, concerned particularly with long-term studies of calcium, phosphorus, magnesium, zinc, fluoride, and iron. The minimum duration of

each study is 30 days, but the studies are frequently carried out for many months. In addition to studies on the metabolism of any given single mineral or trace element, the main emphasis of the investigations is on the availability and interaction of certain minerals with other minerals, and of minerals with trace elements. Extensive studies are carried out on changes of mineral metabolism with aging, which is one of the selected priorities of VA research, and on the calcium requirement. The results of studies under way in this unit are among those being used by the Food and Nutrition Board in its deliberations that will result in the 1985 Recommended Daily Allowance (RDA) for calcium. Studies such as those being carried out in units like Dr. Spencer's are crucial to such deliberations.

Other studies of mineral and trace element metabolism (i.e., calcium, magnesium, zinc, and fluoride metabolism) are carried out in this unit on patients with chronic renal failure who do not receive any medications and are not undergoing dialysis.

3. Research under way at Dr. Marcel Conrad's unit at the VA Medical Center in Birmingham, Alabama, focuses on iron absorption, excretion and metabolism and especially on the mechanisms by which the intestinal mucosal cell regulates absorption of iron and other divalent metal cations. Ferrous and ferric iron complexes within intestinal absorptive cells are identified using electron microscopy; all identifiable iron is measured. The quantity of iron in intestinal absorptive cells varies directly with the status of iron absorption. The postulate as to how this works is being tested by direct-staining electron microscopy; current efforts attempt to develop chemical methods that permit the measurement of the non-ferritin total iron binding capacity and the unsaturated iron binding capacity of the intestinal mucosa.

4. Dr. James Anderson at the Lexington, Kentucky, VA Medical Center is studying the role of plant fiber intake in the management of the metabolic disorders common among veteran patients. Fiber intake has been shown to benefit patients with diabetes mellitus, obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, or reactive hypoglycemia. Since 1974 the metabolic effects of fiber-rich foods on the physiology and metabolism of nutrients in humans and animals have been examined. Initial studies measured the plant fiber content of common American foods, while later studies examined the short-term effects of fiber intake on nitrogen balance and short-chain fatty acid production, as well as the long-term safety and nutritional effects of high-fiber diets.

Current research on the effect of a high-carbohydrate, high-fiber (HCF) diet on patients with diabetes has shown that insulin requirements of lean adults are 75 percent lower than the requirements for patients on the conventional diabetic diets, and weight-reducing HCF diets lower insulin needs of obese patients by 88 percent. HCF diets also appear to lower serum cholesterol concentrations by 30 percent, and fasting serum triglyceride concentrations by 14 percent.

The data show that a high fiber intake lowers postprandial plasma glucose concentrations, increases tissue insulin receptor number, facilitates

intracellular glucose metabolism, and attenuates hepatic gluconeogenesis via short-chain fatty acid release from the colon. The high fiber intake complements the effects of complex carbohydrate intake and fat-restricted diets.

In studies on obesity, the high fiber, weight-reducing diets are accompanied by greater satiety and less hunger than are the low fiber, weight-reducing diets providing equivalent energy. Compared to very low calorie diets, the HCF weight-reducing diets produce less nitrogen loss, less hepatic dysfunction, less ketonemia, and smaller rises in serum uric acid concentrations. The long-term effectiveness of these HCF diets on weight loss is being assessed. Sucrose polyester, a nonabsorbable fat in the form of mayonnaise or margarine, appears to complement the effectiveness of HCF weight-reducing diets.

For patients on the Special Diagnostic and Treatment Unit, with average fasting serum triglyceride concentrations exceeding 1000 mg/dl, weight-maintaining HCF diets lower triglycerides by 80 percent. A long-term intake of high fiber diets lowers fasting serum triglycerides by another 10 percent, so that these patients sustain triglycerides which are 90 percent lower than their initial values.

Other studies have shown that water-soluble fiber has hypocholesterolemic effects. After examining the palatability and effectiveness of several water-soluble fibers and high soluble fiber foods, the effects of oat bran are of particular interest. Oat bran intake selectively lowers serum low density lipoprotein (LDL) cholesterol concentrations without altering serum high density lipoprotein (HDL) cholesterol concentrations, and therefore increases the HDL to LDL cholesterol ratio by 50 percent over short-term periods and by 100 percent over long-term periods. A daily intake of 100 g of oat bran lowers serum cholesterol concentrations by 20 percent without any alteration in the intake of fat or cholesterol. Oat bran intake also increases fecal bile acid excretion by 50 percent. Animal studies suggest that short-chain fatty acids absorbed from the colon attenuate hepatic cholesterol synthesis.

Preliminary studies indicate that high carbohydrate-high fiber diets lower average blood pressures by 10 percent. This reduction may be related to increased fecal electrolyte excretion or reductions in the antinatriuretic effects of insulin. In addition, high fiber diets, low in simple sugar content, correct reactive hypoglycemia of the alimentary or diabetic type; they alleviate symptoms and prevent chemical hypoglycemia.

Thus, diets high in plant fiber have important benefits for selected patients with metabolic disorders. The effects of these diets are well described and confirmed throughout the world, however, the mechanisms responsible for these effects have not been delineated. The long-term effects of fiber intake on mineral balance have not been determined. Collaborative studies are in progress to address some of these major questions.

5. Research conducted by Drs. Neville Colman and Victor Herbert at the Hematology and Nutrition and Hematopathology Laboratories at the Bronx,

New York VA Medical Center primarily involves studies of hematologic nutrition, particularly folate and vitamin B₁₂ status, with respect to their food sources, absorption, transport, and utilization, as well as their binding proteins.

A study on the effect of milk proteins on folate absorption is based on data indicating that folate uptake by isolated rat gut cells is enhanced up to 20-fold by binding to proteins from either liquid or powdered milks. The milk factor that enhances folate uptake by intestinal cells has been partially characterized, and the conditions that allow folate uptake to be enhanced up to 20-fold with human milk and 22-fold with bovine milk have been established. Little damage has been found with pasteurization (with folate binding capacity 72-100% that of raw milk and uptake enhanced 68-93% that of raw milk); and similarly, "ultra-high temperature" (UHT) treatment of milk did not significantly damage the folate-uptake-enhancing ability.

The studies are aimed at characterizing this folate uptake process and determining its clinical significance. Cells that have taken up folate from milk have been compared with those exposed to free folate solutions, with respect to subcellular localization and cellular metabolism of folates. The effect of milk processing on the proteins involved in the process have been examined, focusing on the possible effect of pasteurization on proteins involved in folate uptake. Animal studies are now under way to determine the clinical impact of milk on folate absorption by in vivo assessment.

Studies are also under way to elucidate the mechanism for frequent folate deficiency in the elderly. In one set of studies, healthy institutionalized and free living subjects over the age of 65 are compared with subjects under 35 years of age with respect to dietary intake of folate, and other factors known to have secondary effects on folate metabolism, such as zinc. Concurrent dietary histories are taken to determine whether they can be linked to objective evidence of dietary insufficiency. In other studies, possible absorptive defects in the elderly are being investigated by intestinal perfusion of different folates in subjects over 65, with the results to be compared with data previously obtained in younger subjects.

Several subjects with the rare disorder, congenital folate malabsorption, have been studied since these patients present at 2-3 months of age with severe megaloblastic anemia and varying degrees of permanent mental retardation despite treatment with folic acid. Findings from one patient indicate that medicinal folic acid (pteroylglutamic acid - oxidized folic acid), when given orally or parenterally was less well transported into spinal fluid than folinic acid given parenterally. Folinic acid treatment improved the patient's status and provided protection against the development of mental retardation (in contrast to her sibling who died undiagnosed at the age of 3 months). The continuation of this new therapy with folinic acid (rather than the old therapy with folic acid) hopefully will result in the patient's continued development with no neurological damage.

Preliminary reports have shown that radioassays using pure intrinsic factor occasionally "diagnose" clinical B₁₂ deficiency where it does not exist. Five different radioassays, plus microbiological assays with L. leichmannii and E. gracilis, are being used in an attempt to determine whether an assay for serum B₁₂ levels is available which uniformly correlates with the clinical status with respect to vitamin B₁₂.

A newly discovered abnormal R binder with high specificity for cobalamin in the gastric juice of patients with pernicious anemia has been characterized and is being studied further. Production of this "cobalamin-specific R binder" from saliva R binder by incubation with pancreatic enzymes has been demonstrated. Followup studies are under way in order to determine whether this newly discovered binder plays a role in the more rapid development of pernicious anemia in patients who lose gastric acid production. Studies on vitamin B₁₂ analogues have shown these analogues to exist in human blood cells, liver, and brain. The B₁₂ analogues from five patients having a mean daily bile excretion of 0.89 ug analogue and .65 ug cobalamin equaled 32 percent of serum total corrinoids but 60 percent of dialyzed bile total corrinoids. These findings suggest that the analogue is delivered to the bile preferentially over cobalamin, and that the purpose of the enterohepatic circulation of the vitamin may be to filter potentially noxious cobalamin analogues into the stool while allowing excellent reabsorption of intact cobalamin.

Studies on the amount of vitamin B₁₂ analogues in the multivitamin/mineral supplements containing vitamin B₁₂ that are taken by approximately 100 million Americans daily, have shown that 10 to 30 percent of the designated amount of B₁₂ was actually analogues. In one study, published in the New England Journal of Medicine (July 22, 1982), the standard U.S. Pharmacopeia (USP) assay (L. leichmannii) used by all pharmaceutical firms was shown to be misleading, since L. leichmannii appeared to grow on some analogues that are not cobalamins. The nature and significance of these analogues is currently being studied, particularly in terms of their vitamin B₁₂ activity or anti-vitamin activity in human cells.

6. Three studies under way in the Laboratory of Liver Diseases and Nutrition and the Alcohol Research Center at the Bronx, New York, VA Medical Center, under the direction of Dr. Charles Lieber, are investigating drug and ethanol induced alterations of hepatic vitamin A and associated liver changes, the alteration of amino acid and protein metabolism in the alcoholic, and the liquid diet alcohol feeding technique.

The aims of the first study are to determine 1) whether patients who are treated with drugs or consume alcohol have altered hepatic vitamin A levels, 2) whether drugs induce abnormalities of vitamin A metabolism in the liver that might contribute to the lowering of hepatic vitamin A levels and 3) whether there is an associated deleterious effect on the liver.

Experimental models are used to determine possible mechanisms whereby drug administration can lower hepatic vitamin A, e.g., through bile excretion and increased metabolism of retinoic acid in induced microsomes. The possibility of a selected interaction of retinoic acid with some specific

forms of cytochrome P-450 is being evaluated. The possible role of lowered hepatic vitamin A in the pathogenesis of liver disorders is being assessed.

In studies on the alteration of amino acid and protein metabolism in the alcoholic, they were found to have decreased plasma levels of tryptophan, the serotonin precursor, and a decreased ratio of tryptophan over other amino acids competing for transport into the brain. The plasma of rats and baboons with a carefully controlled alcohol and dietary intake showed a decrease in the ratio of tryptophan over competing amino acids, resulting mostly from increases in valine in the rat, and in valine, leucine, and isoleucine in the baboon. Decreases in the brain tryptophan and serotonin were noted; central serotonin deficiency may contribute to the depressive states frequently seen in alcoholics. Rats fed alcohol chronically showed an increase in tryptophan pyrrolase activity in the liver and an increase in the formation of kynurenine after tryptophan load, thereby explaining in part the depressed plasma tryptophan levels observed.

Other plasma amino acid abnormalities are frequently reported in alcoholics with the most common abnormalities being those of decreased levels of branched chain amino acids (BCAA) due in part to portal-systemic shunting, hyperinsulinemia, hyperglucagonemia, and dietary protein deficiency as well as increased aromatic amino acids. Chronic alcohol consumption also results in increased levels of alpha amino-n-butyric acid, a non-essential amino acid derived primarily from the catabolism of methionine, threonine, and serine, and which may reflect altered glutathione metabolism and lipid peroxidation due to alcohol.

Some limited patient studies and theoretical considerations of amino acid metabolism in patients with hepatic encephalopathy have led to the proposal that dietary protein derived from a vegetable source may be better tolerated and more efficacious in such patients. However, studies in normal humans have revealed that vegetable protein is not as nitrogen sparing as animal protein. These observations led to the study on the effects of vegetable and animal protein sources in patients with hepatic encephalopathy with respect to mental status, nitrogen balance, and plasma amino acids levels under metabolic ward conditions. No significant differences with respect to any of the parameters studied were observed in relationship to the source of dietary protein, but compliance to the regime was much more difficult with the vegetable protein diet.

Many of the ongoing and planned studies involved the application of feeding alcohol as part of a total liquid diet, a technique that results in much higher ethanol intake than with conventional procedures. This kind of feeding reproduced in animal models the following complications usually observed in alcoholics: fatty liver, hyperlipidemia, various metabolic and endocrine disorders, tolerance to ethanol and other drugs, physical dependence and withdrawal, the fetal alcohol syndrome in the rat, and liver fibrosis and cirrhosis in the baboon.

Variations of the liquid diet formulation are being compared and three standardized basic formulas are being proposed for the rat: A) a regular diet, comparable to the diet previously referred to as the "Lieber-DeCarli

Formula" and suitable for most experimental applications, particularly those intended to mimic the clinical situation in which the various effects of alcohol occur in the setting of liver changes characterized by a fatty liver, B) a low fat diet comparable in all respects to the preceding diet but with a lower fat content, intended to minimize the hepatic changes, and C) a high protein formula particularly useful in those circumstances in which an oversupply of dietary protein might be recommended (i.e., pregnancy and lactation).

7. The Nutrition Research Program at the Little Rock, Arkansas, VA Hospital, under the direction of Dr. David Lipschitz, primarily studies nutritional aspects of the aging process. Particular attention is focused on the development of appropriate standards for nutritional assessment of the elderly; documentation of the prevalence and severity of protein-calorie malnutrition in home-based, institutionalized, and ill elderly; the reversibility of protein-calorie malnutrition by appropriate nutritional intervention; and finally the interrelationship between nutrition, age, and host defense.

Studies on the development of appropriate standards for nutritional status assessment have shown that a large number of the nutritional assessment measurements are related directly to height. Examples include the calculation of ideal body weight for height, and the determination of the creatinine-height index. The reduction in height which occurs with aging creates an additional variable in the development of appropriate standards for the elderly. Investigators therefore examined the use of arm length measurements as an alternative to height in nutritional status assessment methods. Long bone measurements were determined in 100 young and 62 aged but healthy individuals; a highly significant correlation between height and total arm length was found. Compared to young subjects, arm measurements for the elderly are shifted significantly upwards, thus demonstrating a reduction in height not paralleled by decreases in arm length. This work confirms the previous observation that while height decreases with age, arm length remains constant. Thus, in the development of the nutritional assessment standards for the elderly, arm length will provide a more accurate reflection of stature than does height.

A second study considered the effect of age and sex on the routinely employed measurements used to assess the nutritional status of hospitalized patients. The various nutritional status assessment measurements studied included tricep skin fold measurements, arm muscle circumference, percent ideal body weight, creatinine height index, creatinine excretion to total arm length, total iron binding capacity (TIBC), hemoglobin and hematocrit levels, and serum albumin levels. Results from the study indicate a great need for establishing suitable standards for the elderly, since many of the parameters differed according to age. For example, the TIBC was significantly lower in healthy elderly females than in healthy young females, due to the elder's higher tissue iron stores and not differences in nutritional status.

The nutritional support of elderly subjects with severe protein-calorie malnutrition (PCM) has been studied. Extensive experience in the diagnosis

of severe PCM in the elderly has demonstrated that primary PCM in hospitalized patients is quite frequent. Subjects enter the hospital with confusion and infection. Diagnosis of PCM is frequently missed, while attention is focused on the overt reason for hospitalization. A marked improvement in the nutritional status of these patients has been shown with enteral hyperalimentation; the patients gain weight and show significant increases in serum albumin and TIBC. In 80 percent of the subjects followed for a 6-week period, hemoglobin improved, the lymphocyte count invariably rose, and anergy was corrected indicating that PCM in the elderly is correctable. Furthermore, the fact that host defense parameters, that are usually ascribed to the aging process, are substantially improved by appropriate nutritional support suggests strongly that nutritional status may play a role in these abnormalities.

Another study involved a complete nutritional status evaluation of 65 indigent elderly subjects participating in the "Meals on Wheels" program. A dietary history and physical examination was performed with the dietary history taken on multiple days by the recall technique and blood drawn for a complete hematologic, nutritional, and immune system function evaluation. In addition, intradermal skin tests were applied and induration was read at 24 and 48 hours.

A few subjects had serum albumin values less than 4.0 g/dl, and 90 percent had values greater than 3.5 g/dl. Many subjects had other evidence suggestive of PCM, i.e., 35 percent had a dietary intake which was less than 70 percent of the Recommended Daily Allowances for protein and calories. Anergy and lymphocytopenia was present in 45 percent of subjects and the total iron binding capacity was reduced in 35 percent. Anemia was present in 20 percent of males and 16 percent of females, although the etiology in the majority was not iron deficiency, folate deficiency, or chronic disease.

From this group of 65 subjects, 12 subjects were selected based upon a high risk of the presence of PCM and monitored for a 3-week control period during which time they were seen at least 3 times weekly. After obtaining baseline data, the subjects were given cans of commercially available polymeric dietary supplement (Ensure Plus) of varying flavors and instructed to attempt to drink 1 can containing 350 Kcal in the midmorning, midafternoon and late evening. A delivered meal was usually received at lunch time.

A significant increase in total caloric intake was clearly documented in all subjects and was maintained for at least a 16-week period. The amount of calories consumed voluntarily remained constant, and an additional 30 to 60 percent of total calories was derived from the use of supplement. Of the 12 subjects examined, a significant increase in weight (greater than 2 kg) was seen in 7. In addition to subjective improvement, some nutritional measurements also showed a marked improvement, i.e., serum albumin showed a modest increase, and TIBC was significantly elevated, red cell and serum folate levels were significantly elevated, and leukocyte ascorbic acid levels were markedly increased. In contrast, no increase in circulating zinc and copper levels occurred and immunologic function did not improve. In addition, this study

indicated that many apparently malnourished subjects fail to gain weight. Two possibilities explaining this phenomenon might be that the subjects are not malnourished and the increase in weight may not parallel calorie intake with an increased food intake if dissipated by increased activity or increased thermogenesis, both basally and following meals, or that food absorption and utilization by the subjects may be abnormal.

Another study of moderately or severely malnourished elderly subjects admitted to research beds of the GRECC (Geriatric Research Education and Clinical Care) Unit of the Little Rock VA Hospital is now under way to examine the effects of food supplementation on moderately malnourished elderly individuals. Metabolic and physiological responses to significant increases in food intake are being monitored by the documentation of calories, changes in weight, anthropometric measurements, and radiographic and radio isotopic determinations of body composition. These studies provide a rational approach to the nutritional support of elderly individuals.

Ongoing studies have demonstrated that anemia is frequent in the elderly. It is associated with an overall reduction in hematopoiesis caused by a decrease in hematopoietic stem cell reserve. Although the abnormality may be related to the aging process, a yet to be defined, potentially reversible abnormality may be present since intensive nutritional support appears to return hematopoietic and stem cell number to normal. This finding strongly suggests that nutritional status may contribute to the defect.

8. Nutrition research at the Nashville, Tennessee, VA Medical Center focuses on nutritional status assessment studies, particularly of folate, thiamin, and vitamin A. The NIH-supported CNRU at Vanderbilt has provided a focus for coordinating human nutrition research with a metabolic assessment laboratory supported by the CNRU serving as a resource for some of the VA studies.

Basic studies being carried out at the Nashville VA include studies on the cellular folate binding proteins and folate metabolism, and on thiamin metabolism. Clinical studies investigate the role of vitamin A in preventing cancer, and the assessment of nutritional status in patients receiving total parenteral nutrition.

Investigators have found two major folate binding proteins in rat liver mitochondria, which have been purified to homogeneity and characterized. The major folate binding protein in the liver cytosol has properties that suggest its possible involvement in the storage of folate, while the two folate binding proteins in mitochondria appear to be enzymes involved in the turnover of choline.

Other studies investigate folate transport into the liver. The uptake of 5-methyltetrahydrofolate by the liver is an energy dependent, active process that can be stimulated by conditions which decrease the redox potential of the system. This finding is significant because alcohol ingestion results in a decreased redox potential in the cell and also causes a more rapid uptake of 5-methyltetrahydrofolate by liver cells.

Recent studies on thiamin metabolism indicate that therapeutic doses of vitamin B₁ prevents lead poisoning in animals and therefore suggests that this naturally occurring compound may have potential therapeutic value in the treatment of lead poisoning in both humans and livestock. The mechanism by which this action occurs is under investigation.

Other reports have shown the existence of a genetic abnormality in the thiamin-requiring enzyme transketolase in patients with Wernicke-Korsakoff syndrome. The abnormality of this enzyme appears to diminish the binding of thiamin pyrophosphate to the apoenzyme. Thus, these individuals have a much higher requirement for thiamin than normal controls, and in times of stress, such as with alcoholism, liver, and kidney diseases, a neuropathy similar to that observed in thiamin deficiency results. Full characterization of both the normal and abnormal enzyme would permit the development of methods to identify those individuals in whom this abnormality is manifest.

Since vitamin A is required to maintain normal epithelial cell differentiation, a number of studies are examining the use of vitamin A as an agent for preventing cancer. The most likely mechanism of action for vitamin A is that when it is complexed with a cytoplasmic binding protein it affects nuclear transcription. VA investigators are measuring and comparing the amounts of cytoplasmic retinoid binding proteins in several types of human skin tumors and in adjacent normal skin. Preliminary data indicate that basal cell carcinomas have 2 to 3 times as much retinoid binding proteins as surrounding normal tissue. This increase may explain why many basal cell carcinomas regress when treated with topical or oral vitamin A analogues.

An assessment of the nutritional status of 1225 patients admitted to the Nashville VA Medical Center has been carried out and compared with the hospital course of these patients. Preliminary data suggest that the serum albumin levels obtained on admission are a good predictive indicator of the subsequent development of complications. In addition, there appears to be a positive correlation between serum albumin, anthropometric measurements, delayed hypersensitivity reactions, lymphocyte count and weight loss. Approximately 30 percent of all patients exhibited an abnormal deficit in at least one nutritional parameter.

A study including 108 patients has also been initiated to determine the effects of total parenteral nutrition (TPN) on various parameters of nutritional status in VA patients. An initial assessment of nutritional status was made either before or immediately after TPN was started, and a followup analysis has been carried out on 20 individuals at various times following TPN therapy in order to determine its effectiveness. These data will be analyzed to determine the optimal parameters to be used in the evaluation of nutritional status and to learn about the effectiveness of TPN in reversing the laboratory indicators of malnutrition.

INTERNATIONAL DEVELOPMENT COOPERATIVE ADMINISTRATION,
AGENCY FOR INTERNATIONAL DEVELOPMENT (IDCA-AID)

The AID nutrition program places highest priority on alleviating under-nutrition through sectoral programs in agriculture, health, food aid, population and education as well as directly through nutrition projects. AID's nutrition research strategy focuses on providing knowledge and developing technologies that will influence nutrition policy in developing countries, especially programs that will impact on infants, young children, and pregnant and lactating women. AID supports research in: developing effective interventions to combat vitamin A deficiency and iron deficiency anemia; improvement of publicly supported food programs; perfecting nutrition planning, education and evaluation methodologies; assessment of new cereal and legume varieties and new low cost foods in human subjects; development of appropriate nutrition surveillance methodologies; the determination of impairment of biological and behavioral function associated with gradient levels of undernutrition.

The nutrition research supported by AID during FY 1980-1982 can be categorized within the following priority areas: nutrition requirements in terms of prevention and treatment of malnutrition; nutrition status and dietary intake-surveys and surveillance; food sciences--new and modified food sources, fortification of foods, and supplements; effects of government policy on diet and nutrition; and international nutrition education activities.

Nutrition Requirements in terms of Prevention and Treatment of Malnutrition

A major research activity was undertaken at the end of FY 1981 as a Collaborative Research Support Program under Title XII of the Foreign Assistance Act. The project is designed to study the effect of marginal food intake on selected physiological and behavioral functions. Six U.S. universities are involved conducting field research in Egypt, Kenya, and Mexico in collaboration with national institutions.

Early cessation of breast-feeding and inappropriate weaning practices are associated with increased infant illness and death, particularly in low income communities in developing countries. A project has been initiated to focus on three aspects of these problems: preventing a major decline in breast-feeding that could undermine nutrition and health of infants, improving maternal nutrition, and improving the diets of infants during the transition from breast-feeding to other foods in the first 2 years of life. Research continues to assess the determinants of infant feeding trends.

Several models have been designed to predict the outcome of the "nutrition system". All of the models are similar in their essential elements. However, the complexity of the interactions of factors (food supply, income, health, and education) that lead to malnutrition are insufficiently understood to permit adequately detailed modeling. More field work to evaluate existing programs is required before an adequate understanding of the interactions of these factors can be obtained for planning and management purposes. At present, AID has completed a critical review of the literature and two contractors who have been selected to conduct this

work have begun developing detailed work plans.

Nutritional Status and Dietary Intake - Surveys and Surveillance

Most developing countries do not have adequate information on the extent, nature, and/or causes of malnutrition in their populations. The design of effective nutrition policies and programs or their evaluation is, therefore, not possible. AID, in collaboration with CDC, supports studies to develop and test simplified survey methods for assessing nutritional status and dietary intake that are also applicable to nutritional status surveillance. Using these simplified methods, AID has supported a project of national nutritional status assessment and dietary surveys of preschool children in Cameroon, Egypt, Haiti, Lesotho, Liberia, Nepal, Sierra Leone, Sri Lanka, Togo, and Yemen. The project, in close collaboration with U.N. agencies, emphasizes the development of appropriate nutrition surveillance methods and continues to assist additional countries in developing baseline descriptions of their nutritional status through surveys. This project also currently supports surveillance activities in El Salvador, Haiti, the Philippines, and Sri Lanka. Survey and surveillance consultations have been provided to Bolivia, Costa Rica, Indonesia, Kenya, Malawi, Morocco, Niger, Swaziland, Zaire, the Organization for Economic Cooperation and Development (OECD), and the Kampuchea Task Force.

Future plans for this project call for comprehensive assistance in the design and testing of national nutrition surveillance systems in Haiti, Kenya, Morocco, the Philippines, and one other country yet to be selected. Consultation will be provided to five additional countries. Surveillance training programs and workshops will be supported in three other countries. Two survey manuals and one surveillance manual being developed in collaboration with CDC will be published and disseminated.

Each host country provides personnel, logistical support, and partial funding of field work, and assumes responsibility for the conduct of follow-up tasks based on the information developed by the surveys and surveillance activities. Other supporters of these activities include the U.S. Peace Corps, Catholic Relief Services (CRS), Cooperative for American Relief Everywhere (CARE), Food and Agricultural Organization (FAO), United Nations International Children's Emergency Fund (UNICEF), the World Bank, and WHO. Close coordination will continue between AID and United Nations agencies' that support nutrition surveillance efforts in developing countries.

Food Sciences--New and Modified Food Sources, Fortification of Foods, and Supplements

Iron deficiency anemia is one of the more prevalent nutritional deficiencies in the developing world, second only to protein-calorie malnutrition. Its harmful consequences are felt especially by young infants, growing children, adolescents, and pregnant women. AID provides funds and technical support to several research organizations in the U.S. and in developing countries as a portion of the U.S. contribution to a global effort to alleviate this preventable condition.

AID has responded to requests by individual countries for consultation by arranging short-term visits by experts through the International Nutritional Anemia Consultative Group (INACG), an international group composed of donor agencies, industry representatives, and scientists concerned with iron deficiency anemia. Cameroon, the Caribbean, Egypt, Guatemala, Guyana, Indonesia, the Philippines, and Thailand have been visited. Also participating in INACG and supporting projects to combat iron deficiency anemia are UNICEF, WHO, and other donors.

An extensive and detailed field study of a new iron fortificant for food, iron EDTA, nears completion. This source of supplemental iron has particular relevance and applicability to diets in the less developed countries. This study is one of the few extensive field tests of a potential iron fortificant delivery system. If successful, iron EDTA is likely to have widespread applicability to iron fortification of centrally processed staples.

Preliminary results suggest that the ingestion of soy protein by humans partially inhibits the absorption of iron from diets. If this finding is confirmed, collaborative studies of this problem will be undertaken by the concerned agencies in the U.S. and elsewhere. Recently, DOD, DHHS-FDA, and USDA in conjunction with AID supported the INACG in assembling a task force of experts to address this problem.

Under an AID nutrition loan the Chilean government has developed two unique procedures in combating iron deficiency anemia in infants and school children: one procedure involves an acidified milk powder fortified with iron and vitamin C, and the other a fortified cookie. Field studies have shown the products to be efficacious. The Chilean government has requested the INACG to review both fortification programs for technical merit and to develop guidelines for the future monitoring of each system of fortification.

Over 250,000 preschool children in developing countries become blind each year from vitamin A deficiency. In 1974, the United States joined in an international effort to substantially reduce blindness from this cause. In the same year, AID sponsored a major conference on vitamin A deficiency during which experts from AID, WHO, and 12 developing countries re-examined vitamin A deficiency and discussed possible intervention strategies. In 1976, AID sponsored the establishment of the International Vitamin A Consultative Group (IVACG), composed of experts from developing countries, AID, U.N. agencies, and others concerned with this nutrition problem. Professional guidance is provided by IVACG to locally and internationally sponsored programs in developing countries; IVACG also develops guidelines for future programs. Special training in vitamin A deficiency problems has been provided by AID to 12 physicians, half from developing countries, who are now participating in vitamin A programs.

In addition, AID has assisted Egypt, El Salvador, Haiti, Indonesia, the Philippines, and Sri Lanka in the conduct of national vitamin A deficiency prevalence surveys and has completed initial assessments of vitamin A status in Cameroon and Yemen. With AID financing, WHO has recently completed initial assessments of the vitamin A deficiency problem in

Benin, Ethiopia, Mali, Malawi, Oman, Somalia, Sudan, and Upper Volta. Currently, AID is assisting national programs for the control of vitamin A deficiency in Bangladesh, Guatemala, Haiti, Honduras, India, Indonesia, and Sri Lanka. The NIH National Eye Institute, WHO, FAO, UNICEF, governments of Great Britain and the Netherlands, and Helen Keller International, Inc. are also contributing to vitamin A deficiency alleviation projects in a number of developing countries.

New crop varieties and newly developed low cost nutritious foods must be evaluated in humans for their nutritive value and safety before being introduced into worldwide use. One clinical laboratory in Peru is supported by AID to conduct such tests. Since many of the new low cost nutritious foods and new cereals and legumes may find use in weaning foods, it is particularly important that these new food products be fully tested in infants and young children, under standardized conditions. For example, recent tests of whole grain sorghum flour have shown that it is very poorly digested by infants and young children and is of apparently very low protein quality. Further studies are to be conducted on variously processed sorghum flour. Test data on white potatoes suggest that they could be a useful component in a blended weaning food in some developing countries, and work in this direction is continuing. In previous years, this Peruvian clinical laboratory participated in the development of the low cost corn-soy-milk and wheat-soy-blend products that are used in the Foods for Peace program as well as in other developing countries' food programs. This program has also supported research that compares the nutritional merit of different varieties of wheat, rice, and other cereals. Testing of rice varieties and new blended foods continues, since cereals generally are inadequate as sole sources of protein for infants and young children.

Effects of Governmental Policy on Diet and Nutrition

Although the nutritional well being of individuals in the developing countries is often related to agricultural policies, AID is concerned that such government policies and programs are often designed and implemented with little consideration given to their ultimate nutritional impact. Consequently, AID has initiated a project to: (1) provide policy-makers with better methods for projecting the probable effects of various agricultural policy choices on people's food consumption patterns and nutrient intakes; (2) test and empirically demonstrate the validity of the prediction methods in several developing countries; (3) disseminate information concerning these methods to planners in developing countries through expert consultants, seminars, workshops, and an information network; and (4) encourage planners, as they formulate agricultural policies, to adopt and use these methods so as to give careful consideration to nutrition and food consumption effects.

It is anticipated that by FY 1983 the project will have completed a group of six short-term impact studies designed to evaluate the effect of food, feed, and cash or export crop production on consumption and nutrition in Botswana, Cameroon, Jamaica, Senegal, Sudan, and Tanzania. A longer term collaborative study in Honduras should be half completed. Also by FY 1983, the information network will have been established and several seminars conducted.

Seed funds were provided by AID to the International Agricultural Research Centers in order to encourage the Centers to evaluate the inclusion of nutrition considerations and nutrient analysis into their agricultural programs, either within their institutions or in collaboration with nutrition institutes. To date, programs have been established at two Centers, the International Rice Research Center (IRRI) and the Asian Vegetable Research and Development Center (AVRDC). The project at IRRI is a collaborative program with the Food and Nutrition Research Institute in Manila to clinically evaluate the nutritional value of new varieties of rice developed by IRRI. The AVRDC project focuses on using nutrition as a means of promoting the utilization of AVRDC products; to that end, a nutritionist has been added to the Center's staff.

A government's economic policies may have as great an effect on food consumption behavior and nutrition as the agricultural policies described above. Therefore, AID has initiated a project that aims to: (1) develop and test methods for predicting household food consumption behavior, particularly for low income households that produce a significant portion of their own food; and (2) develop and test procedures for utilizing predictors of food consumption behavior in order to project the effects of changes in income, prices, or employment on nutrient intake. To date, completed field work in Sierra Leone has obtained needed data on the nutritional status and food behavior of rural people. Analyses of the data and characterization of the food consumption patterns and their variation with changing prices and income are underway.

International Nutrition Education Activities

In addition to being active in the four research areas described above, AID supports programs in international nutrition education carried out in developing countries. Two nutrition education programs supported by AID complement its nutrition research activities. One of the education programs is designed to improve the effectiveness of nutrition education efforts directed at the populations of developing countries; the other is aimed at middle and senior level staff of the governments of developing countries to foster the inclusion of nutrition planning in agricultural and rural development projects.

In recent years the developing countries have expressed growing interest in incorporating nutrition education as a component of nutrition, education, and agriculture projects. Recent AID grants and World Bank loans have included a nutrition education component. However, traditional methods of nutrition education have been costly and time consuming and have not significantly decreased the incidence of malnutrition in the developing countries. It is believed by AID that this lack of success may be due in part to the fact that effective mass media techniques have not been widely used to reach large segments of nutritionally vulnerable people in developing countries. From its experience with other education efforts designed to promote behavioral changes, AID has gained considerable knowledge that could be applied to nutrition education. Therefore, AID initiated a project in late 1979 to provide participating countries an opportunity to improve their (1) use of mass media techniques for nutrition education, (2) use of the community participation approach to

plan and implement nutrition education projects, (3) design of messages at village level, (4) use of social marketing techniques to sell basic nutritional concepts, and (5) design of integrated national nutrition education strategies and their entire nutrition education systems.

In addition, AID makes appropriate technical assistance and training available to developing countries to enable them to design, implement, and evaluate nutrition education programs. Host countries contribute to project costs and provide logistical support for in-country training efforts. To date, technical assistance has been provided to the 17 developing countries and AID missions that have requested it.

Since 1974, AID has been sponsoring a series of nutrition planning workshops. These workshops, designed for host government staff, representatives of private voluntary organizations, and AID employees, are given by universities, private consulting firms, and government supported nutrition institutes in the less developed countries. In the past 3 years, these workshops have emphasized the identification of third world institutions that can sponsor such training and provide field experience to the participants with minimal AID assistance.

Previous AID training programs have focused on the need for multisectorial nutrition planning. Countries are now asking for courses to provide their staff with specific nutrition program management skills and AID is responding to these requests by redirecting its short-term nutrition planning programs. Therefore, future AID programs will emphasize nutritional knowledge and program management techniques. In addition, AID is sponsoring training on planning and implementing programs that will have a positive nutritional impact on food consumption by the poor; these programs respond to the needs of agricultural and rural development project officers from both the developing countries and AID staff. International organizations such as FAO are working closely with AID to incorporate nutrition concerns into agricultural training programs. Host countries contribute to project costs and provide logistical support for in-country training programs.

DEPARTMENT OF DEFENSE (DOD)

DOD priorities in human nutrition research are incorporated as components of various basic and applied mission-oriented research and development programs. This research is under way as components of the Navy Medical Research and Development Command (NMRDC) programs, the U.S. Army Medical Research and Development Command (USAMRDC) programs, and the U.S. Army Natick Research and Development Laboratories (NLABS) programs.

Research with a nutrition component conducted as part of the NMRDC mission includes studies to evaluate the effectiveness of various fluid supplements, with different electrolyte concentrations, to minimize the hypohydration that frequently occurs during heavy physical exercise in cold climates, as well as studies on the effect of prolonged periods (2-3 months) of submarine deployment on serum levels of trace elements and vitamins D and C.

Nutrition research supported by the USAMRDC includes studies to define the effects of thermal injury on endocrine function and the metabolism of proteins, carbohydrates, and fats as well as the effects of infectious diseases on protein metabolism. These studies also include the development and assessment of various nutritional support therapies. For example, studies carried out at the U.S. Army Institute for Surgical Research in San Antonio, Texas, have provided important information on the optimal nutritional support of soldiers with burn injuries. A highlight of this research has been the development of a computer graphics program used for the rapid evaluation of the nutritional status of critically ill burn patients, and for the subsequent tailoring of parenteral and/or enteral diets for the specific patient. At the U.S. Army Medical Research Institute of Infectious Disease, at Fort Detrick, Maryland, other studies are under way on the development of appropriate nutritional therapy to reduce protein wasting associated with infectious diseases.

The DOD Food Research Program, located at the U.S. Army Natick Laboratories, is a multidisciplinary research program that incorporates food and behavioral sciences approaches to evaluate the effects of new food processing techniques and long-term storage on food acceptance, nutrient content, and bioavailability of nutrients in foods used for military rations. In conjunction with this research, the U.S. Army Research Institute of Environmental Medicine, also at Natick, has become a primary focal point for the military nutrition research directed specifically to nutrition-related problems on tomorrow's battlefield, and the subsequent development of appropriate military combat rations and other feeding regimens. The critical end-point of this research is the effective performance of military-related physical and mental tasks carried out under sustained combat operations in all environmental conditions.

In order to help plan for these research efforts, a Committee on Military Nutrition Research has been established with the Food and Nutrition Board, National Research Council, National Academy of Sciences (FNB/NRC/NAS) under contract with the USAMRDC. The purpose of the committee is to advise the USAMRDC on critical nutrition factors that may influence military performance and to recommend appropriate areas of research

emphasis that would address the relationship of diet and nutritional status to military performance. In addition, a close liaison is being established with the human nutrition research programs of USDA and other Federal agencies in the hopes of developing, without duplication of efforts, a nutrition research technology base.

DOD supports workshops and other meetings that address the nutrient needs of the military, and publishes reports on various aspects of nutrition that relate to the DOD's research missions.

In FY 1982, the first meeting of the NATO Panel VIII, Research Study Group 8, "Nutritional Aspects of Military Feeding," was held in Natick, MA. Representatives of the military nutrition programs under way in the United Kingdom, Canada, Netherlands, Belgium, Federal Republic of Germany, France, and the United States were present to promote active collaboration of military nutrition research and to foster nutrition research methods acceptable to member countries.

A workshop on the "Nutritional Requirements of Military Personnel in Protective Clothing," held in Washington, D.C., was supported by the USAMRDC and conducted by the FNB/NRC. The objective of this workshop was to provide a preliminary assessment of the problems of thermal load and body fluid and electrolyte deficits that may occur during continuous wear of protective clothing for periods of 24 hours. The workshop provided guidance regarding both the quantity and nutrient composition of replacement fluids which should be consumed to maintain adequate performance of mental and physical tasks. Recommendations were also provided on the research required to evaluate the effectiveness of the proposed nutrient solutions.

An excellent example of interagency cooperation was the preparation and publication of the report of the International Nutritional Anemia Consultative Group on "The Effects of Cereals and Legumes on Iron Availability," June 1982. This report, prepared through a grant from USAMRDC and supported jointly by NLABS, USDA, FDA and USAID, concluded that there is a decrease in the total amount of iron absorbed from a meal when soy protein is used as a meat extender. Part of the reduction in iron absorption is due to a decrease in the heme iron content of the meal, part due to an inhibitory effect of soy, and part to a decrease in the enhancing effect of meat on the absorption of non-heme iron. In population groups where nutritional iron deficiency is uncommon (e.g., adult males and post-menopausal women), the substitution of up to 30 percent of the meat with soy products should pose few problems relative to iron nutrition. In other groups where iron nutrition may be marginal (e.g., infants, children, young women), the use of up to 30 percent soy substitution for several meals per week is justifiable if there are adequate amounts of meat, fish, poultry and ascorbic acid in the diet. Cereal-soy blended foods used to help alleviate malnutrition in populations at greatest risk of iron deficiency should be fortified with an adequate amount of stabilized ascorbic acid in order to more effectively enhance the bioavailability of fortification iron. Specifically, the report noted that the present levels of soy-extended beef being used in military feeding systems and school lunch programs should pose no problems if the diet contains enhancers of iron bioavailability in adequate amounts.

NATIONAL SCIENCE FOUNDATION (NSF)

Following the initiation of the Human Nutrition Research Program in FY 1979, nutrition research carried out by NSF during FY 1980 under this program attempted to determine the nutritional impact on humans of changes in foods that result from refining, cooking, packaging, storage, and any other processing methods. Approximately \$1.2 million dollars was budgeted for this research in FY 1980 through the Division of Problem Focused Research; this support was later decreased to \$970,000 by a deferral.

Due to a reorganization of NSF in FY 1981, the Human Nutrition Research Program was discontinued and the budget provided for no new research projects. Only those human nutrition research projects awarded in years prior to FY 1981 continued to receive support.

DEPARTMENT OF COMMERCE,
NATIONAL OCEANIC AND ATMOSPHERIC ADMINISTRATION (DOC-NOAA)

DOC-NOAA, the major agency with responsibility for fish and fishery products, has a modest effort in human nutrition research that attempts to respond to identified needs expressed by both consumer groups and the seafood processing industry for information on the nutritional value of seafoods. In FY 1980-82, three studies, funded by the National Marine Fisheries Service, were concluded: a 2-year study on the effects of cooking and processing on the nutrient composition of certain species of fish and shellfish; a 4-year study on the safety of partially hydrogenated menhaden oil when used directly in human food; and a survey to obtain seafood consumption data.

JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH (JSHNR)
of
Committee on Health & Medicine (CHM)
and Committee on Food & Renewable Resources (CFRR)
Federal Coordinating Council for Science
Engineering & Technology (FCCSET)

CHARTER

Because of the vital importance of the benefits from human nutrition research to the welfare of the American people and the world population, it is essential that the nutrition research efforts of the Federal agencies be mutually reinforcing.

In recognition of this need, the Committee on Health and Medicine (CHM) and the Committee on Food and Renewable Resources (CFRR) hereby establish a Joint Subcommittee on Human Nutrition Research (JSHNR).

Scope: The Subcommittee is concerned with: (1) all federally supported or conducted research on nutrition with emphasis on human nutrition; and (2) professional personnel needs in nutrition research and education. This includes:

- o Basic physiological and biochemical mechanisms for the digestion, absorption, metabolism, and transport of nutrients; the role of food ingredients in human health and performance and in the prevention and treatment of disease.
- o Nutrient composition of foods; the effects of storage, processing, and packaging; and the biological availability of nutrients in the foods at the time of consumption.
- o Determinants of dietary practices and methods for educating the public about dietary practices.
- o Food consumption patterns and nutritional status of the general population and of special high-risk subgroups within the population; evaluation of the nutritional impacts of various intervention strategies and public policies.
- o The professional personnel to carry out research on human nutrition; training programs in nutrition research and nutrition education in medical schools, dental schools, schools for allied health professionals, schools of nutrition, teachers' colleges, and schools of food and agriculture; nutrition education at the primary and secondary school level; and the manpower needs for education of the public.

Purpose and Function: The purpose of JSHNR is to increase the overall effectiveness and productivity of research efforts in nutrition. In fulfilling this purpose, the Subcommittee will:

- a. Improve planning, coordination, and communication among Federal agencies engaged in research on nutrition.
- b. Develop and update plans for Federal research programs to meet current and future domestic and international needs for nutrition.
- c. Collect, compile, and disseminate information on nutrition research.
- d. Prepare reports describing activities, findings, and recommendations of the Subcommittee.

Organization of the Committee

The Co-Chairpersons of JSHNR will serve a term of two years and be selected by mutual agreement between the Chairpersons of CHM and CFRR. The Executive Secretary will be designated by the Co-Chairpersons of the Subcommittee (JSHNR). Chairpersons of task forces or working groups of the Subcommittee will arrange for staff assistance from their own agencies.

In addition to the Co-Chairpersons, the Subcommittee will include representation from:

- o Agency for International Development
- o Department of Agriculture
- o Department of Commerce (NOAA)
- o Department of Defense
- o Department of Health, Education, and Welfare
- o Federal Trade Commission
- o National Science Foundation
- o Veterans Administration
- o Office of Science and Technology Policy -- ex officio

Other Federal agencies may participate, as appropriate, upon invitation by the JSHNR Co-Chairpersons.

The Subcommittee will follow a schedule of periodic meetings and hold special meetings at the call of the Co-Chairpersons. Agendas for meetings will be made available for members prior to each meeting. Minutes of meetings will be prepared by the Executive Secretary and distributed to all members of the Subcommittee, to leaders of its task forces or working groups, and to the Executive Secretary of FCCSET, CHM, and CFRR.

The Subcommittee will have such task forces or working groups as established by the Co-Chairpersons for the conduct of required Subcommittee work.

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be full-time Federal employees who are allowed reimbursement by their agencies plus per diem for subsistence while their duty stations in accordance with Standard Government

Annual Cost Estimates

Estimated annual cost of operating the Subcommittee, excluding staff support, is \$1,000. Estimated annual cost of staff support is one person-year at \$20,000.

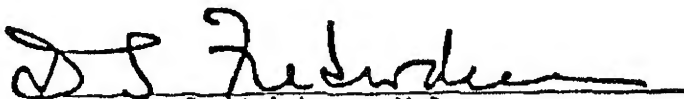
Reports


The Subcommittee shall prepare a report for the Chairperson of FCCSET, CHM, and CFRR not later than sixty days after the end of each fiscal year. This report shall contain as a minimum the Subcommittee's functions, a list of members and their business addresses, the dates and places of meetings, and a summary of the Subcommittee's activities and recommendations during the year.

Determination

I hereby determine that the formation of the Subcommittee on Human Nutrition Research is in the public interest in connection with the performance of duties imposed on the Executive Branch by law, and that such duties can best be performed through the advice and counsel of such a group.

Approved:


Donald S. Fredrickson, M.D.
Chairman
Committee on Health and Medicine

 DAVID G. UNGER
M. Rupert Cutler
Chairman
Committee on Food and Renewable Resources

SEP 28 1978

DATE


Frank Press
Chairman
Federal Coordinating Council for
Science, Engineering, & Technology

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JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH

AGENCY REPRESENTATIVES

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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20500

February 5, 1982

The Honorable Charles A. Bowsher
Comptroller General of the United States
Washington, DC 20548

Dear Mr. Bowsher:

I am pleased to comment on the GAO draft report "Progress in Federal Human Nutrition Research Should Continue with Planning and Coordination Improvements."

This draft report reviews the recent history of coordination efforts among the major federal agencies involved in human nutrition research and proposes steps to continue, extend, and formalize those efforts. I am pleased that the report recognizes the excellent progress made during the last five years in coordination of federal human nutrition research activities, the lead role played by the Office of Science and Technology Policy (OSTP) in that progress, and the commitment and hard work of the members of the Joint Subcommittee on Human Nutrition Research (JSHNR) as evidenced in their December 1980 report on human nutrition research and training.

The draft GAO report contains two recommendations to the Director of OSTP. The first recommendation is for the Director of OSTP to direct the JSHNR to develop a federal nutrition research plan by developing specific goals for federal human nutrition research programs, and by identifying the responsibilities of the federal departments and agencies and the resources and time required to accomplish those goals. I concur in principle with this recommendation and perceive it to be consistent with the policies of this Administration and the intention of the members of the Joint Subcommittee. That Subcommittee has demonstrated its commitment to effective coordination by: agreeing on a common definition of human nutrition research; describing the existing nutrition research activities and expenditures of federal departments and agencies; identifying critical research issues; preparing reports on international nutrition research and nutrition education and professional manpower; organizing a conference to discuss research progress and identify research needs; and developing a common computerized data retrieval system.

These varied activities provide the groundwork for improved planning of federal human nutrition research. It is the intention of the JSHNR to update and expand its 1980 report and to use that report as the vehicle for evolving a broad federal nutrition research plan within which the individual agencies can develop separate plans consistent with their legislated responsibilities and missions. To the degree possible and appropriate, the federal plan will delineate agency responsibilities and necessary resources. We agree that the process of preparing such a plan will greatly enhance federal nutrition research programs.

The second GAO recommendation to the Director of OSTP urges that, in developing a nutrition research management system, external input be broadly solicited. I concur fully in this recommendation and will encourage the members of the JSHNR to follow through in their plan to involve the various relevant external communities in the development and implementation of the data retrieval system now envisioned.

One other comment. On page 23, the text indicates that an OSTP official referred to the cost of JSHNR activities as "minimal." I wish to clarify that the term "minimal" was meant to refer to the direct cost of these activities to OSTP. Since the responsibility for the operation of the JSHNR is assigned to the agencies, our costs are minimal. However, the cost to the agencies is considerable. Those who believe in, and encourage, greater cooperation and coordination among federal agencies should understand that such efforts are not without cost. Effective coordination requires a significant commitment of time and energy -- real and opportunity costs which must be taken into account when considering the imposition of new coordination mechanisms and planning activities.

Sincerely,

A handwritten signature in dark ink, appearing to read 'G. A. Keyworth', with a long horizontal flourish extending to the right.

G. A. Keyworth for
Science Advisor to the President

Congressman Brown's Keynote Address to the JSHNR
Conference of Federally Supported Human Nutrition Research Units,
December 16, 1982

I am pleased to participate in this First Annual Conference of Federal Human Nutrition Research Units. Since the expected outcomes of the conference are "To increase coordination and collaboration among the agencies and thereby enhance planning for nutrition research at the Federal level," I assume you do not totally disagree with the current emphasis I have urged the Science Committee and the Agriculture Committee to place on nutrition research and comprehensive planning. On the other hand, your invitation for me to speak here this morning may have resulted from concerns that the mechanisms the Committees hoped would motivate research planning and implementation are either ineffective or unnecessary. If this is the case, I especially appreciate the opportunity to be here so that we may exchange viewpoints, and I can learn from the nutrition experts assembled here today.

Let me begin by expressing my views on the role of planning in advancing the frontiers of science and technology and on the importance of several components of planning. As you well know, Congress has not demonstrated outstanding expertise in either coordination or planning. In fact, the frequently disparate Congressional directives resulting from overlapping jurisdictional boundaries of numerous Committees, and the disruption caused by budgetary uncertainty have no doubt hindered your ability to implement your own near-term goals. Unfortunately, this situation is not likely to change in the immediate future. Although that realization may neither be a surprise nor an encouragement to you, it does demonstrate the need for scientists in government, academia, and industry to jointly develop a comprehensive plan to guide research initiatives in nutrition as well as to guide policy-makers.

Dr. Simopoulos has commented on some of my Subcommittee involvement in nutrition. While the Subcommittees' jurisdictions are fragmented and irrational, the individuals on the Subcommittees tend to try to integrate these various jurisdictional conflicts into some sort of a coordinated whole. In terms of my role on both the Agriculture Committee and the Science Committee: I have served on both these Committees for many years and I have maintained and developed a continuing interest in this general problem of how to more effectively coordinate and plan for scientific research in a variety of fields. I try to address this problem in any Subcommittee that I may chair in a particular session of Congress. During this session, I chaired the Agriculture Subcommittee, dealing with Department Operations, Research, and Foreign Agriculture (DORFA). In the last session, it was the Science Committee's Subcommittee on Science, Research, and Technology (SRT), and before that, it was the Science Subcommittee now entitled the Subcommittee on Natural Resources, Agricultural Research, and the Environment.

In all of these Subcommittees, there are members who have an interest in the general health of research, and how it could be better organized. What generally results is the emergence of some kind of consensus among those Subcommittee members that there are certain things that need to be done. Generally speaking, this has led to an emphasis on developing

coordinated research plans where you have research that is being conducted throughout the government which is complex, frequently multidisciplinary, and cuts across jurisdictional boundaries. That is the generic problem that you are seeking to address with this conference today.

I am convinced that a nutrition research plan developed and accepted by representatives of the broad range of disciplines which encompass the science and the application of nutrition would play a major role in advancing the state-of-the-art and emphasizing to policy-makers and to the public the need for sustained and continuous support. You may not care about the quality of research, but I know you care about sustained support. You have to see the relationship between having a coordinated approach and sustained and continuous support. Organized and coordinated views which result from the process of planning are imperative to the development of a consensus which guides public policy and related budgetary actions.

I know that you must be familiar with similar planning efforts in other research areas. For example, the coordinated toxicology program that runs across the government was developed for the same reason. And, the National Climate Program Act exists for the purpose of bringing together climate research activities, a fairly esoteric field. That Act is embodied in a special piece of legislation. There are numerous other examples of efforts to pull together a framework for similar kinds of complex programs. There is no magic solution. I cannot tell you what is the best way to develop the plan, but I can tell you that rational people perceive the need for rational guidance to these kinds of programs, and they want tools to guide them. And, those tools are the plans that you are going to be working on.

Thus, I am very pleased that Dr. Keyworth has accepted the recommendations of the May 1982 GAO report that he "Direct the Joint Subcommittee on Human Nutrition Research to develop a Federal nutrition research plan." This conference is subtitled "An Information Exchange Activity of the Joint Subcommittee" and is a necessary component of a coordinated and comprehensive research plan. However, I trust that following this conference the Joint Subcommittee and all of you here today will be ready to move beyond information exchange, definitions of nutrition research, identification of priority research activities, and research classification systems and data elements to the process of developing a comprehensive plan for action. During this process you can waste a lot of time, i.e., you can spend a lot of time working on the details that I have enumerated today, and forget that the larger goal is to develop a plan to guide resources and to use them in developing answers to problems.

Finally, I was somewhat surprised to learn that these components of Federal nutrition research management and planning were not in place at the establishment of the Joint Subcommittee. I was also surprised to learn during my 1981 DORFA Subcommittee hearing on nutrition research that a management information system for human nutrition research did not exist at the Federal level or that the Executive Branch did not

categorize nutrition research expenditures by Agency and area of support on a systematic basis. The lack of an on-line system and the fact that the data could not be compiled until nine months or more after the close of a fiscal year, prompted me to introduce the mandate for a "Plan for a Human Nutrition Research and Information Management System" in the Agriculture and Food Act of 1981.

I can assure you that this will be a continuing mandate, i.e., the same or stronger language will be in the Agriculture Act of 1985, the Act of 1989, and so on into perpetuity. I have been putting this kind of language, with successive refinement, into a wide range of legislation for many years. For example, I am sure you know that similar language pertaining to all of science exists in the Science Policy Act that mandates the Five Year Outlook for Science and Technology as a whole. Similar language also exists with regard to resource planning in the Forestry Act and many other Acts. This action results not only from my personal interest, although I have been involved in all of these aforementioned Acts, but from the growing awareness of many Members of Congress that only this kind of approach will allow the Congress to measure results, to make wise decisions about allocating resources, and so on.

I understand the development of the Plan for a Human Nutrition Research and Information Management System, not to mention the implementation, was not a simple task. Let me assure you that the process of developing a comprehensive human nutrition research plan will be even more difficult and frustrating. The planning process will not be successful or productive if controversies do not arise over the planning strategy itself; i.e., who will and should undertake this planning and its implementation, what are the future perspectives and trends, and how much planning is needed to direct change.

All of you know that planning is controversial and sometimes even polarizing, and I don't want to focus on that aspect of planning. I don't want this plan to become controversial and polarizing; the reason why this often results is due to the planning process itself. Some planning is antidemocratic, authoritarian, dictatorial, and counterproductive. I don't want to see that happen in any kind of planning that involves science. Other planning is participatory, it involves the best thinking of the user group, the client group, or all people who have something at stake. This kind of planning seeks to integrate their views into a purposeful program which aids the planning process. That is the kind of planning that we need to look at. It is not so much the concept, but the fact that people frequently do not distinguish between good democratic planning and bad authoritarian planning. This is what we need to be concerned with.

It would appear that before a comprehensive plan for Federal human nutrition research can be developed that two complex policy questions need to be articulated:

1. What should the Nation's human nutrition research goals be and what benefits to society can be realized by achieving these goals?

2. What role should the Federal government play, versus other sectors of society, in achieving these national human nutrition research goals?

These are both very fundamental policy questions you need to ask yourselves. They are generic. We are asking ourselves these questions not only about nutrition research; just yesterday we visited with the Director of the National Science Foundation and we raised these same questions about science education, engineering research, and a whole host of other similar issues. We need to keep these questions before us at all times.

Unless national goals and the relative roles of the various sectors of society are defined, it will be difficult, if not impossible, to develop a meaningful plan for the Federal nutrition research module and select an effective planning mechanism. However, the planning mechanism you choose should provide a means to move beyond conflicts over assumptions, biases, and turfs to realistic choices through workable compromises. To be effective, the planning process must be viewed as an experimental process and unsuccessful trials as learning experiences just as they are in the research and development processes.

I am surprised sometimes that scientists cannot seem to understand that most of the institutional experimentation they conduct should be regarded as a scientific process, in the same way as the research they conduct in a particular physical field. In fact, Congressmen should recognize that most of what we do is a scientific experiment, but because we do not recognize this we make a lot of mistakes, or fail to learn from our mistakes. You are much too smart to do that. You are certainly more intelligent than Congressmen, and I urge you to keep that point in mind.

Our similar effort in the climate research program, which I was involved with beginning several years ago, started with innumerable difficulties in making the proper institutional arrangements to do what you are trying to do. You might learn from analyzing the mistakes that have been made in the climate program, and see if you can go through the learning curve more rapidly as a result of that experience.

In order to obtain understanding and support for the priorities and expected outcomes of the plan, the planning process must also accommodate broad participation and provide for open communication about goals and assumptions. I believe experience has slowly taught us that decentralized or logical unit planning can more readily incorporate future needs and opportunities. Thus, perhaps GAO was correct in calling for a Federal nutrition research plan before a National plan is formulated. Even the Federal component may have to be developed through the integration of logical unit subsets or through interlocking research modules.

Whatever the Federal planning strategy, I believe the academic and private sectors should be involved in the process. This component is important to delineate the priorities of these groups and identify those activities which they can prepare to undertake to achieve National goals. This process will also assist in gaining their support and understanding of the Federal plan and the priorities which are identified as the necessary

and proper role of Federal nutrition research programs. From my optimistic viewpoint, the objective of this broad participatory planning would be to motivate university, industry, professional, and consumer coalitions to join with the Federal government in developing not only National nutrition research goals, but ultimately a National nutrition research plan. Such a plan might also serve to identify the roles of the various players, who is best suited to undertake the responsibilities, and the resources required to achieve the specified outcomes and their contributions to societal goals.

It is obvious that the ultimate role of nutrition research is to get human beings to act more rational in terms of dietary intake. If the public is not involved in that process of determining the rational goals, then you are going to have a very difficult time getting them to do anything about it. This point seems so clear that it does not have to be belabored. Many times the public will allow the experts to come up with something that is absolutely letter perfect, and they'll tell you that they are not interested because you have not consulted with them and they really don't care very much about your expertise. I know that they treat politicians that way.

Regardless of whether the plan focuses on Federal nutrition research or on a more comprehensive framework, the resulting plan will be of limited value if viewed as a statement of policy to be defended against all adversaries. The role of the plan is that of consensus building and of a communication tool to its designers and constituents expressing an affirmation of goals and principles. Adjustment of the plan as conditions and perceptions change is a part of the process and should not be perceived as inconsistency or lack of foresight. The planning process, in spite of its frustrations, can be as important as the resulting document.

A comprehensive research plan, regardless of the discipline involved, is not the sole answer to generating new knowledge and creating appropriate mechanisms for putting that knowledge to use for the benefit of society. However, such a plan is certain to influence and assist the scientific community in addressing national needs and identifying opportunities to improve the flow of ideas between the laboratory, the marketplace, and the consumer. Hopefully, such a plan would also assist the Congress and the Executive Branch to move from today's preoccupation with budgets and administration to the role of science in addressing the Nation's economic problems and enhancing the quality of life. If some of you ever thought that we support science for any other reasons, you should change that perception. We have a very pragmatic approach to the support of science--either it does good for people, or we do not support it.

The plan I envision is not intended to be a mechanism for controlling nutrition research or dictating specific research activities which should be pursued by the implementors. Rather, the plan should serve as a guide for directing and motivating research that would achieve comprehensive nutrition goals as defined by the leaders of the numerous disciplines which encompass the science and application of nutrition. The plan must be sufficiently flexible to tap the creativity of individuals, maintain the integrity of the scientific process, and encourage centers of excellence.

I realize that the development of a comprehensive plan is not a simple or easy task. I also realize that there are few, if any, models to draw upon from other disciplines. However, I believe that nutrition has a major role to play in identifying the causes and the solutions to many of today's and tomorrow's health, economic, and social problems.

I am convinced that the science of nutrition has the potential to demonstrate the benefits of focusing a major portion of health related research on behavior modification and disease prevention rather than on treatment, and to set examples of how other areas of science and technology can plan to more effectively deliver the products and services they offer society. The need for the continuation of basic research in relationship to prevention goals is well understood. However, to effectively implement the current concepts of "wellness," increased emphasis must be placed on research at the interface between biomedical and behavioral methodologies. How can we expect to modify behavior if we do not know the basis for such addictions as overeating and smoking, or the effects of stress on health? Likewise, social science research can make significant contributions to health, e.g., finding effective ways to communicate nutrition research results in a manner that would truly influence lifestyles.

I hope that I have convinced you through my simplistic, optimistic, and frequently dogmatic view of planning and priority-setting, to accept the challenge to place nutrition in the forefront of scientific leadership. I look forward to the results of both the planning process and the planning document. I trust that the outcomes will be a valuable experience for you and that you will discover new ways to generate a concept of priorities through a systematic process. Your success will challenge other coalitions of scientists, entists and Federal agencies to experiment with the models you discovered and thus improve the effectiveness of both science and science planning.

It is even conceivable that your planning demonstration may help this Administration and those that follow to better understand the contributions of the social and behavioral aspects of nutrition and the importance of integrating food science, nutrition, and health research. I also trust that your planning demonstration will help to emphasize the importance of the National Nutrition Monitoring System. Surveillance and monitoring, including epidemiological investigations, are basic and essential to insuring the safety and quality of the food supply, to assuring that the nutritional needs of the public are met, and to assuring that an appropriate data base exists for planning future research needs and guiding the expenditure of public funds for nutrition research, programs, and intervention. Current budgetary actions proposed by OMB for these types of programs in agencies such as CDC, FDA, and HNIS indicate that this educational process is badly needed.

Let me emphasize that I attach a great deal of importance to what you are doing. I am interested in the process, the framework, and the implications of what you are doing in terms of improving man's process of and making use of that knowledge. I will be closely. I am a politician, and frequently a main concern with my role is whether it will contribute to the welfare of this country. I have a similar attitude with regard to your work.

Tables of Expenditures by Federal Agencies in Human Nutrition Research,
Manpower Development, Training, and Education,
FY 1979 - 1981

TABLE VII

FY 1979 Expenditures by Federal Agencies in Human Nutrition Research,
Manpower Development, Training, and Education, by Area of Support
(in thousands of dollars)

Agency	Extramural Research	Research Manpower Development	Intramural Research	Research Training	Research on Public Education & Inform.	Total
DOC	266					266
DOD			2,420		180	2,600
DHHS: NIH	122,474	1,570	6,116	4,037	125	
ADAMHA	4,465	1,022	68	160		
FDA	2,549		1,109		323	
Other	470					
	<u>129,958</u>	<u>2,592</u>	<u>7,293</u>	<u>4,197</u>	<u>448</u>	144,488
FTC					30	30
IDCA-AID	1,605					1,605
NASA	910		700			1,610
NSF	2,730					2,730
USDA	12,400		18,700		8,400	39,500
VA			2,500			2,500
TOTAL	<u>147,869</u>	<u>2,592</u>	<u>31,613</u>	<u>4,197</u>	<u>9,058</u>	<u>195,329</u>

TABLE VIII

FY 1979 Human Nutrition Research Expenditures of Federal Agencies by Support Mechanism
(In thousands of dollars)

Department	Extramural			Intramural		Total
	Grants (competitive)	Contracts (competitive)	Interagency Agreements	Cooperative Agreements	Intra- mural	
DOC	53		213			266 (0.1%)
DOD					2,420	2,420 (1%)
DHHS:	NIH	24,756	713		6,116	
	ADAMHA	5,487			68	
	FDA	2,149	400		1,109 ⁰	
	Other	470				
	<u>104,114</u>	<u>27,375</u>	<u>1,113</u>		<u>7,293</u>	139,895 (77%)
FTC						0
IDCA-AID	100*	582 449* <u>1,031</u>	474			1,605 (1%)
NASA	205	571	175		700	1,651 (1%)
NSF	2,730					2,730 (2%)
USDA	5,000	2,996	4	3,200	15,500	31,100 (17%)
VA					2,500	2,500 (1%)
TOTAL	<u>112,202</u> (61%)	<u>31,973</u> (18%)	<u>1,979</u> (1%)	<u>3,200</u> (2%)	<u>28,413</u> (16%)	<u>182,167</u> (100%)

* Non-competitive

TABLE IX

FY 1980 Expenditures by Federal Agencies in Human Nutrition Research,
Manpower Development, Training, and Education, by Area of Support
(in thousands of dollars)

Agency	Extramural Research	Research Manpower Development	Intramural Research	Research Training	Research on Public Infor- mation and Education	Total	
DOC	175				5	180	0.1%
DOD	100		2,224		100	2,424	1.2%
DHHS: NIH	126,032	1,207	7,759	3,829	294†	[139,121	67.2%]
ADAMHA	3,696	295	691	1,352		[6,034	2.9%]
FDA	1,365		2,652*		303	[4,320	2.1%]
CDC					716	[716	0.3%]
HSA	373					[373	0.2%]
DHHS Total	<u>131,466</u>	<u>1,502</u>	<u>11,102</u>	<u>5,181</u>	<u>1,313</u>	<u>150,564</u>	<u>72.8%</u>
FTC					21	21	0.1%
IDCA-AID	2,812				350	3,162	1.5%
NASA	307		457			764	0.4%
NSF	2,123				35	2,158	1.0%
USDA	9,231		26,119		9,726	45,076	21.8%
VA			2,500		77	2,577	1.2%
TOTAL	<u>146,214</u>	<u>1,502</u>	<u>42,402</u>	<u>5,181</u>	<u>11,627</u>	<u>206,926</u>	
	70.7%	0.7%	20.5%	2.5%	5.6%	100%	

* Represents 98 person-years of effort.

† \$7,685,000 devoted to nutrition education research is included in other categories, primarily Extramural Research, for comparability with FY 1979 tabulations.

TABLE X

FY 1980 Human Nutrition Research* and Training Expenditures of Federal Agencies by Support Mechanism
(In thousands of dollars)

Department	Extramural			Intramural		Total
	Grants (competitive)	Contracts (competitive)	Interagency Agreements	Cooperative Agreements	Intra- mural	
DOC	120	55				175 <.1%
DOD			100		2,224	2,324 1.2%
DHHS: NIH	116,305	13,160	1,626		7,736	[138,827 71.1%]
ADAMH	5,343				691	[6,034 3.1%]
FDA		1,085	280		2,652@	[4,017 2.1%]
HSA	373				373	[373 0.2%]
DHHS Total	<u>122,021</u>	<u>14,245</u>	<u>1,906</u>		<u>11,079</u>	<u>149,251 76.4%</u>
IDCA-AID	1,473†	1,339				2,812 1.4%
NASA	187	20	100		457	764 0.4%
NSF	2,123					2,123 1.1%
USDA	3,500	1,483		4,477	21,642	35,350 18.1%
VA					2,500	2,500 1.3%
TOTAL	<u>129,424</u>	<u>17,142</u>	<u>2,106</u>	<u>4,477</u>	<u>37,902</u>	<u>195,299 100%</u>
	66.3%	8.8%	1.1%	2.3%	19.4%	100%

* Excludes research on Public Information and Education

† Non-competitive

@ Represents 98 person-years of effort

TABLE XI

FY 1981 Expenditures by Federal Agencies in Human Nutrition Research,
Manpower Development, Training, and Education, by Area of Support
(in thousands of dollars)

Agency	Extramural Research	Research Manpower Development	Intramural Research	Research Training	Research on Public Infor- mation and Education	Total	
DOC	953					953	0.4%
DOD	28		1,653			1,681	0.8%
DHHS: NIH	130,814	1,310	9,893	3,709	2,775	[148,601	68%]
ADAMHA	4,861§		633§			[5,494§	2.5%]
FDA	243		4,974*		175	[5,392	2.5%]
CDC					716	[716	0.3%]
HSA	67					[67	<.1%]
HHS Total	135,985	1,310	15,500	3,709	3,666	160,170	73%
TC						0	0%
DCA-AID	2,783				926	3,709	2%
ISA	212		162			374	0.2%
IF	1,298§					1,298§	0.6%
DA	11,101		27,627		8,400	47,128	22%
			2,500		77	2,577	1%
TOTAL	152,360	1,310	47,442	3,709	13,069	217,890	100%
	70%	0.6%	22%	2%	6%	100%	

§ represents 115 person-years of effort.
* preliminary figures

TABLE XII

FY 1981 Human Nutrition Research* and Training Expenditures of Federal Agencies by Support Mechanism
(In thousands of dollars)

Department	Extramural			Intramural		Total
	Grants (competitive)	Contracts (competitive)	Interagency Agreements	Formula Grants	Cooperative Agreements	Intra- mural
DOC	534	419				953 0.5%
DOD			28			1,653 0.8%
DHHS: NIH	118,090	16,425	1,319			9,893 [145,727 71%]
ADAMHA	4,861§					633 [5,494§ 3%]
FDA		88	155			4,974@ [5,217 3%]
HSA		67				[67 <0.1%]
DHHS Total	<u>122,951</u>	<u>16,580</u>	<u>1,474</u>			<u>15,500</u> [156,505 77%]
IDCA-AID		855				
IDCA-AID total	846†	<u>1,021†</u> <u>1,876</u>	61			2,783 1%
NASA	150	56	61			429 0.2%
NSF	1,298§					1,298§ 0.6%
USDA	3,427	3,004		4,670	1,719	25,908 38,728 19%
VA						
TOTAL	<u>129,206</u>	<u>21,935</u>	<u>1,624</u>	<u>4,670</u>	<u>1,719</u>	<u>2,500</u> 2,500 1%
	63%	11%	0.8%	2%	0.8%	22% 204,877 100%
						100%

* Excludes research on Public Information and Education

† Non-competitive

@ Represents 115 person-years of effort

§ Preliminary figures

Definition of human nutrition research

"Human nutrition research" is the pursuit of new knowledge to improve the understanding of nutrition as it relates to human health and disease and, as here defined, encompasses studies in three major areas: biomedical and behavioral sciences, food sciences, and nutrition education.

Research in the biomedical and behavioral sciences

Studies in the biomedical and behavioral sciences aspect of human nutrition research include: 1) the consequences of food or nutrient intake and its utilization by the intact organism (animal model or human being); and 2) the metabolic and behavioral mechanisms involved. Included are investigations of nutrient variables at the cellular or subcellular level. Also found here are:

- Dietary and nutritional studies expected to produce significant changes in the health status of humans, such as the maintenance of health and the treatment of disease. Such studies might take the form of clinical trials, epidemiological studies, metabolic studies, population surveillance, nutritional status monitoring, or efforts to evaluate various strategies for nutrition intervention and related public policies.

- Studies designed to explain the metabolic role or function of nutrients in humans and in animal models relevant to human nutrition.

- Studies concerned with genetic-nutrient-environmental interactions in humans, where a nutrient is an experimental variable.

- Studies of the interaction of diets and nutrients with toxic materials, manmade or naturally occurring, including drugs and carcinogenic agents.

Research in food sciences

Under the food sciences aspect of human nutrition research fall studies primarily concerned with the nutritional quality, content, or composition of foods, or with the bioavailability of nutrients in foods. Research activities related to the food sciences that are included in human nutrition research are:

- Studies on the nutritional characteristics of foods and diets for human use as influenced by various factors. These include varietal and species differences, harvest and postharvest technology, food processing, transportation, and retail food practices—

when such studies are designed specifically to increase knowledge of human nutrition.

- Studies on methods to improve the speed and accuracy with which food components of nutritional importance are analyzed.

Research in nutrition education

Nutrition education research includes:

- Studies of dietary practices, food consumption patterns, and their determinants.

- Studies on methods for informing and educating the public about nutrition, health, and dietary practices.

HUMAN NUTRITION RESEARCH DATA CLASSIFICATION SYSTEM

This classification system, for use by the Joint Subcommittee for Human Nutrition Research (JSHNR), FCCSET, OSTP, and the Federal Human Nutrition Research and Information Management System was developed based upon the definition of human nutrition research adopted by the JSHNR. The system is designed (when read together with the definition) to permit program managers to classify projects with a minimum of confusion, or questions of definition.

The categories are divided into five major classes: I. Research in the Biomedical and Behavioral Sciences, II. Research in Food Sciences, III. Research on Nutrition Monitoring and Surveillance of Populations, IV. Research in Nutrition Education, and V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition. Classes III and V, not explicit in the definition, have been added to meet the needs of USDA and AID.

The 34 categories permit the classification of any nutrition research project falling within the definition. At least one category must be assigned to each activity. As many classification categories as are needed may be chosen in order to adequately identify all major nutrition aspects of the research activity being classified.

Only the 34 categories with arabic numerals are entered into the data system. The areas (labeled with Roman numbers and upper case letters) and the information in brackets and parentheses is included to structure the classification system for ease of comprehension and thereby facilitate classification.

[I. Research in the Biomedical and Behavioral Sciences]

[A. Research on Normal Nutritional Requirements Throughout the Life Cycle:]

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.]

1. Maternal Nutrition
2. Infant and Child Nutrition (0-12 years)
(includes the low birthweight infant)
3. Adolescent Nutrition (13-18 years)
4. Adult Nutrition (19-65 years)
5. Nutrition of the Elderly (65+ years)

[B. Diseases and Conditions:

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16]

6. Cardiovascular Disease and Nutrition
7. Cancer and Nutrition
8. Other Diseases and Nutrition
(e.g., osteoporosis, diabetes, etc.)
9. Trauma (including Burns) and Nutrition
10. Infection--Immunology and Nutrition
11. Obesity, Anorexia, and Appetite Control
12. Genetics and Nutrition
13. Nutrition and Function
(includes mental, psychomotor, and work performance;
environmental stress)
14. Nutrient Interactions
(includes nutrient-nutrient interactions, nutrient-drug
interactions, nutrient-toxicant interactions, and nutri-
ent toxicity)
15. Other Conditions and Nutrition
16. Nutritional Status
(includes research on methods for the determination of
nutritional status and surveillance: dietary history and
food consumption, biochemical determinants, anthropo-
metry, and clinical examination)

[C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels:

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research, such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.]

17. Carbohydrates
18. Lipids (Fats and Oils)
(includes essential fatty acids, lipo- and apo-proteins)

19. Alcohols
(includes ethanol, sorbitols, and other alcohols used as components in synthetic and semi-synthetic foods)
20. Proteins and Amino Acids
(includes essential as well as non-essential amino acids such as taurine and carnitine)
21. Vitamins
(includes Vitamin A, C, B₆, B₁₂, D, E, K, Thiamin, Riboflavin, Niacin, Folacin, Biotin, and Pantothenic Acid)
22. Minerals and Essential Trace Elements
(includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)
23. Water and Electrolytes
(Includes sodium, potassium, and chloride)
24. Fiber
25. Other Nutrients In Food
(such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin and various growth factors)
- 14*.Nutrient Interactions
(includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)
- 27*.Bioavailability of Nutrients
(includes methods for the determination of bioavailability of nutrients)

[II. Research in Food Sciences:

Categories 26-29 should be used for research in the nutritional aspects of food sciences.]

26. Food Composition
(includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)
27. Bioavailability of Nutrients
(includes methods for the determination of bioavailability of nutrients)

*This category is listed here to indicate that it may also be applicable to research on Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels (Class I.C).

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets
(includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking.)

29. Other Research in Food Sciences

[III. Research on Nutrition Monitoring and Surveillance of Populations]

30. Food Consumptions Surveys
(includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys.)
31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants.
- 16*. Nutritional Status
(includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

[IV. Research on Nutrition Education]

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation
(includes studies on methods for informing and educating professionals in these areas.)

33. Other Research in Nutrition Education

[V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition]

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

category is listed here because it is may also be applicable to
Monitoring and Surveillance of Populations.

P R O G R A MANNUAL CONFERENCE OF FEDERALLY SUPPORTED HUMAN NUTRITION RESEARCH UNITSAN INFORMATION EXCHANGE ACTIVITY OF
THE JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH

of the Committee on Health and Medicine
and the Committee on Food, Agriculture, and Forestry Research
Federal Coordinating Council on Science, Engineering, and Technology
Office of Science and Technology Policy
Executive Office of the President

DECEMBER 16-17, 1982

at the

NATIONAL ACADEMY OF SCIENCES
2101 Constitution Ave, N.W., Washington, D.C.

Members, Joint Subcommittee on Human Nutrition Research:

Department of Health and Human Services:	Artemis P. Simopoulos, M.D. Cochairperson and Executive Secretary
Department of Agriculture:	Mary Carter, Ph.D. Cochairperson (Acting)
Agency for International Development:	Samuel G. Kahn, Ph.D.
Department of Commerce-NOAA:	Thomas J. Billy
Department of Defense:	Lt. Col. David Schnakenberg, Ph.D.
National Science Foundation:	William Van B. Robertson, Ph.D.
Veterans Administration:	Victor Herbert, M.D., J.D.
Office of Science and Technology Policy (ex officio):	Denis J. Prager, Ph.D.

THURSDAY, DECEMBER 16, 1982

NAS Lecture Room

8:30 a.m.	Introductory Remarks	Artemis P. Simopoulos, M.D. Mary Carter, Ph.D. Cochairpersons, JSHNR
	Introduction of Keynote Speaker	Thomas E. Malone, Ph.D. Deputy Director, NIH
8:45	Keynote Speaker	Honorable George E. Brown, Jr. Chairman, Subcommittee on Department Operations, Research & Foreign Agriculture, U.S. House of Representatives
9:15	Discussion	

USDA Program in Human Nutrition Research
Session Chairperson: Mary Carter, Ph.D.

9:45	Overview of USDA Program	Donald Therriault, Ph.D. National Research Program Leader, USDA
	Presentation of Highlights of USDA Research by Directors of Laboratories:	
10:05	James M. Iacono, Ph.D. Western Nutrition Research Center	
10:25	Walter Mertz, Ph.D., Beltsville Human Nutrition Research Center	
10:45	Coffee Break	
11:00	Hamish N. Munro, M.D., Human Nutrition Research Center on Aging	
11:20	Buford L. Nichols, M.D., Children's Nutrition Research Center Baylor College of Medicine	
11:40	Harold Sandstead, M.D., Grand Forks Human Nutrition Research Center	
12:00 p.m.	Discussion	
12:30	Lunch	

DHHS Program in Human Nutrition Research
Session Chairperson: Artemis P. Simopoulos, M.D.

1:30 p.m. Overview of DHHS Program Artemis P. Simopoulos, M.D.
Chairman, Nutrition Coordinating
Committee, NIH

Presentation of Highlights of NIH - Clinical
Nutrition Research Units by Unit Directors:

1:50 Charles E. Butterworth, Jr., M.D., University of Alabama

2:10 Elaine Feldman, M.D., Medical College of Georgia

2:30 Harry Greene, M.D., Vanderbilt University

2:50 Richard S. Rivlin, M.D. Memorial Sloan Kettering Cancer Center

3:10 Irwin H. Rosenberg, M.D., University of Chicago

3:30 Coffee Break

3:45 Earl Shrager, M.D., University of Wisconsin

4:05 Myron Winick, M.D., Columbia University

4:25 Presentation of Highlights of NIH Intramural Research:
Artemis P. Simopoulos, M.D., Chairman, Nutrition Coordinating
Committee, NIH

Helen B. Hubert, Ph.D., M.P.H., Epidemiology & Biometry Program
National Heart, Lung, and Blood Institute, NIH
"Obesity As An Independent Risk Factor For Cardiovascular Disease"

4:45 Discussion

5:15 Overview of FDA Program Alan Forbes, M.D., Assoc.
Director for Nutrition and Food
Sciences, Bureau of Foods, FDA

Presentation of Highlights of FDA Research:

5:30 Nutrition Research, John Vanderveen, Ph.D., Bureau of Foods

6:15 Discussion

6:30 Reception and Buffet

Great Hall, National Academy of Sciences

FRIDAY, DECEMBER 17, 1982

NAS Auditorium

DHHS Program in Human Nutrition Research--continued

Session Chairperson: Artemis P. Simopoulos, M.D.

8:30 a.m. FDA Presentations--continued

Consumer Studies, Raymond Stokes, Ph.D., Bureau of Foods

DOD Programs with Nutrition Research Components

9:00 Presentation of DOD Research Programs with Nutrition Components Lt. Col. David Schnakenberg, Ph.D.
Office of Asst. Surgeon General
for Research and Development, DOD

9:15 Discussion

VA Program in Nutrition Research

Session Chairperson: Victor Herbert, M.D., J.D.

9:30 Overview of VA Program Victor Herbert, M.D., J.D., Chief,
Hematology and Nutrition Lab.
VA Medical Center, Bronx, N.Y.

Presentations of Highlights of VA
Nutrition Research by VA Clinical Investigators:

9:45 James Anderson, M.D., Lexington, KY

10:00 Neville Colman, M.D., Ph.D., Bronx, NY

10:15 Charles Lieber, M.D., Bronx, NY

10:30 Coffee Break

10:45 David Lipschitz, M.D., Little Rock, AR

11:00 Conrad Wagner, Ph.D., Nashville, TN

11:15 Discussion

AID Programs in Human Nutrition Research
Session Chairperson: Samuel Kahn, Ph.D.

11:30 a.m. Overview of AID Programs Samuel Kahn, Ph.D.
Senior Nutrition Advisor, AID

Presentations of Highlights of AID
Nutrition Research Units by Unit Directors:

11:45 International Center for the Control of Nutritional Anemia James D. Cook, M.D.
Kansas University Med. Ctr.

12:00 p.m. International Center for Epidemiologic and Preventative Ophthalmology Alfred Sommer, M.D.
Johns Hopkins University

12:15 Discussion

12:30 Lunch

Summary and Conclusions

Session Cochairpersons: Artemis P. Simopoulos, M.D.
Mary Carter, Ph.D.
Cochairpersons, JSHNR

Discussion of:

1:45 o Identification of Program Strengths and Gaps

2:15 o Research Needs

2:45 o Recommendations for Further Coordination and
Planning Efforts

5:00 Adjournment

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Conference on the Assessment of Nutritional Status

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National Institute of Mental Health

September 16-18, 1981

National Institutes of Health
Building 31C, Room 6
Bethesda, Maryland

Sponsored by:
Centers for Disease Control
Food and Drug Administration
Nutrition Coordinating Committee
of the National Institutes of Health

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

- 8:00 Registration**
- 8:45 Greetings and Introduction**
 Thomas E. Malone
*Acting Director
 National Institutes of Health*
 Artemis P. Simopoulos
*Chairman, Nutrition Coordinating
 Committee—National Institutes of
 Health*
- 9:00 Conference Address**
 Richard S. Schweiker
*Secretary, Department of Health
 and Human Services*
- 9:15 Session 1: Assessment of the Nutritional
 Status of the Individual**
 Cochairmen: Victor Herbert
*Veterans Administration
 Medical Center,
 The Bronx*
 Van S. Hubbard
*National Institutes of
 Health*
**Overview: "Deficiencies of Essential
 Nutrients, Clinical and Biochemical
 Manifestations"**
 Daniel Rudman
Emory University Hospital
- 9:45 Panel Presentations**
**"Malnutrition in the Hospitalized
 Patient"**
 Khursheed N. Jeejeebhoy
Toronto General Hospital
**"Assessment of Nutritional Status
 Prior to Surgery"**
 Josef E. Fischer
*University of Cincinnati Medical
 Center*
- 10:30 Break**
- 10:45 Panel Presentations**
**"Nutritional Assessment of the Pediatric
 Patient Including the Low Birth Weight
 Infant"**
 William C. Heird
*College of Physicians and Surgeons
 of Columbia University*
**"Assessment of the Nutritional Status
 of the Elderly"**
 Barbara A. Bowman
University of Chicago
- 11:30 General Discussion—Invited Discussants**
 Harry L. Greene
*Vanderbilt University School of
 Medicine*
 Charles E. Butterworth
University of Alabama in Birmingham
 Robert M. Russell
*U.S. Department of Agriculture
 Nutrition Research Center at Tufts
 University*
 Ekhard E. Ziegler
University of Iowa School of Medicine
- 1:00 Lunch**
- 2:00 Session 2: New Approaches to Methods
 for the Assessment of Nutritional Status
 of the Individual**
 Cochairmen: Hamish N. Munro
*U.S. Department of
 Agriculture Nutrition
 Research Center at Tufts
 University*
 Theodore B. Van Itallie
*Department of Health
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**Overview: "New Approaches to Body
 Composition"**
 John S. Garrow
*Clinical Research Centre, Harrow,
 England*
- 2:30 Panel Presentations**
**"Transport Proteins as Indices of
 Protein Status"**
 Michael H. N. Golden
University of West Indies
"Estimation of Body Composition"
 (a) **"Some New Approaches Based
 on Total Body Water, Potassium and
 Calcium"**
 Samuel J. Fomon
*University of Iowa
 School of Medicine*
 (b) **"Some New Approaches Based
 on Electromagnetism"**
 Gail Harrison
*University of Arizona College of
 Medicine*
**"Methods for Measuring Body Stores
 Using Serum Ferritin as a Model"**
 James D. Cook
Kansas University Medical Center

- 3:30 Break**
- 3:45 Panel Presentations**
"In Vivo Quantification of Body Nitrogen for Nutritional Assessment"
 Ashok N. Vaswani
Brookhaven National Laboratory
- "Muscle Mass: Reliable Indicator of Protein-Energy Malnutrition Severity and Outcome"**
 Steven B. Heymsfield
Emory University Hospital
- 4:30 General Discussion—Invited Discussants**
 Paul Webb
Webb Associates
 James A. Olson
Iowa State University
 Wesley Harker
Emme Company
 Gilbert B. Forbes
University of Rochester Medical Center

Thursday, September 17

- 8:30 Session 3: Effects of Nutritional Status on Functional States**
 Cochairmen: Jules Hirsch
The Rockefeller University
 Marian R. Yarrow
National Institute of Mental Health
- Overview: "The Interactions of Nutrition and Behavior"**
 Jules Hirsch
The Rockefeller University
- 9:00 Panel Presentations**
"Effects of Nutritional Status on Immunologic Function"
 Susanna Cunningham-Rundles
Memorial Sloan-Kettering Cancer Center
- "The Impact of Micronutrient Status on Behavior in Man: Iron Deficiency as a Model"**
 (a) **"Selection of Optimal Measures of Iron Nutrition"**
 Rudolph L. Leibel
The Rockefeller University
- (b) **"Design of Tests of Cognitive Function for Field Studies of Nutrition—Behavior Interactions"**
 Ernesto Pollitt
University of Texas Health Sciences Center

- 10:00 Break**
- 10:15 Panel Presentations**
"Effects of Carbohydrate and Protein on Work Performance"
 Edward S. Horton
University of Vermont College of Medicine
- "Effects of Nutritional Status on Autonomic Nervous System Function"**
 Lewis Landsberg
Harvard Medical School
- 11:00 General Discussion—Invited Discussants**
 Clement A. Finch
University of Washington
 David E. Barrett
Children's Hospital Medical Center
 Irwin J. Kopin
National Institute of Mental Health
 J. Wesley Alexander
University of Cincinnati Medical Center
- 12:30 Lunch**
- 1:30 Session 4: Assessment of Nutritional Status in Epidemiologic Studies and Surveys of Populations**
 Cochairmen: Alfred E. Harper
University of Wisconsin
 Milton Z. Nichaman
Centers for Disease Control
- Overview: "Issues in the Assessment of Nutritional Status in Populations"**
 Jean-Pierre Habicht
Cornell University
- 2:00 Panel Presentations**
"Methodological Considerations in the NHANES"
 Robert Murphy
National Center for Health Statistics
- "Epidemiological Studies in Pregnant Women, Methodological Considerations"**
 David Rush
Faculty of Medicine, Columbia University
- "Epidemiological Studies in Children, Methodological Considerations"**
 George M. Owen
Bristol-Myers Company
- 3:15 Break**

- 3:30 Panel Presentations**
"Epidemiological Studies in the Young and Middle Age Adults, Methodological Considerations"
 Robert B. McGandy
Tufts University School of Medicine
"Epidemiological Studies in the Elderly, Methodological Considerations"
 A.N. Exton-Smith
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University College London
"Evaluation of Nutrition Intervention Studies, Methodological Considerations"
 George H. Beaton
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- 4:45 General Discussion—Invited Discussants**
 Reuel A. Stallones
University of Texas School of Public Health
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 Marianna K. Fordyce
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Friday, September 18

- 8:30 Session 5: Recent Advances in Food Consumption Methodology**
 Cochairmen: Gilbert A. Levelle
General Foods Technical Center
 Allan L. Forbes
U.S. Food and Drug Administration
Overview: "Measurement of Food Consumption—Past, Present, Future"
 Robert O. Nesheim
Quaker Oats Company
- 9:00 Panel Presentations**
"The USDA National Nutrient Data Bank"
 Frank Hepburn
U.S. Department of Agriculture
"The Classic Approach—The USDA Nationwide Food Consumption Survey"
 D. Mark Hegsted
U.S. Department of Agriculture
"Alternative Approaches to Classic Methods: Telephone Interviewing and Market Data Bases"
 Raymond E. Schucker
U.S. Food and Drug Administration

- 10:00 Break**
- 10:15 Panel Presentations**
"Prediction of Nutritional Status From Food Consumption and Consumer Attitude Data"
 Howard G. Schutz
University of California at Davis
"Food, Eating Habits and Health"
 Horace Schwerin
Campbell Soup Company
- 11:00 General Discussion—Invited Discussants**
 R. Gaurth Hansen
Utah State University
 Arnold E. Schaefer
Swanson Center for Nutrition, Inc.
 Herbert L. Meisselman
U.S. Army Natick Research and Development Laboratories
 James R. Kirk
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- 1:00 Lunch**
- 2:00 Session 6: Summary and Recommendations**
 Cochairmen: Alfred E. Harper
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BACKGROUND

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Office of Cancer Communications

NCI's CHEMOPREVENTION PROGRAM

National Cancer Institute
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The National Cancer Institute (NCI) has developed a new program, called the Chemoprevention Program, to coordinate research exploring the use of natural and synthetic agents in reducing the incidence of cancer.

The goals of the program include finding ways to halt or reverse the development of cancer in people already exposed to cancer-causing agents (carcinogens) or potential carcinogens. This strategy may be particularly beneficial to those people at very high risk for cancer as well as those with certain precancerous conditions that might increase their risk of developing cancer.

The new program was started in response to mounting laboratory and epidemiological studies indicating that various agents could halt or reverse cancer progression in animals or reduce the incidence or risk of cancer in humans. This new research area is based on the recommendations of numerous working groups that met between 1978 and 1981 to investigate the feasibility of a research effort in clinical and experimental chemoprevention. These groups concluded that such a research effort was needed and in September 1980, the chairman of the Board of Scientific Counselors of the Division of Resources, Centers and Community Activities (DRCCA) appointed a subcommittee on chemoprevention. Its mission was to review the state of the art in chemoprevention in the United States and abroad, and to advise the NCI on the feasibility of establishing a major program in this area. This subcommittee met on January 28, 1981, and decided that a group of experts should convene to consider which potential preventive agents should be studied and how the clinical trials should be conducted. These experts met in May, June, and September 1981 and their recommendations were reviewed by DRCCA in setting up the new program.

Information on cancer inhibition has come from studies on laboratory-grown cells, animals, and human populations. These studies have identified two groups of potential chemopreventive agents: (1) naturally occurring substances found in many foods and synthetic compounds considered safe for clinical trials. These include the retinoids--vitamin A and its chemical cousins--and its precursor, beta-carotene. These substances are found in green and yellow vegetables and fruits, in liver, and in dairy products; and (2) agents currently undergoing intensive laboratory study but not yet ready for clinical trials, such as the phenolic antioxidants BHT and BHA, protease inhibitors, prostaglandin synthesis inhibitors, indoles, and uric acid. Other dietary agents that may possibly have a preventive effect are vitamin C (ascorbic acid), abundant in citrus fruits, tomatoes, and vegetables; vitamin E (alpha tocopherol), found in vegetable oils; and the trace metal selenium, found in seafoods, organ meats, and some cereal products.

Many scientists believe that cancer apparently develops in cells as a result of a progression of changes that occur over many years. Many factors, such as exposure to x-rays, sunlight, tobacco smoke, and chemicals, may influence this process. Numerous points may therefore exist at which the process could be interrupted for preventive effects.

Carcinogens such as x-rays and sunlight are associated with free radical reactions capable of altering the cell's DNA. These chemical changes in the DNA alter the cell's normal life and may be related to cancer development. Normal metabolic processes of the digestive tract can convert noncarcinogenic

substances into active forms. Specifically, ingested nitrites can combine in the stomach with amines to form nitrosamines or with amides to form nitrosamides. Nitrosamides are carcinogens and nitrosamines usually require metabolic activation to become carcinogenic. Agents such as beta-carotene, vitamins A, C, and E, and the trace element selenium may prevent, inhibit, or reverse carcinogenesis--possibly by blocking free radical reactions at the cellular level or the formation of nitrosamines in the stomach.

Intake of all vitamins has increased dramatically in the United States since 1975 through the use of vitamin supplements. Nearly 40 percent of adult Americans now take vitamin pills. It is anticipated that NCI will fund future studies of supplement use to determine the possible beneficial effects of the vitamins and possible harm from excessive use. In the meantime, until definitive results of these studies become available, a balanced diet providing the minimal daily requirements of vitamins, minerals and protein, and including ample fresh fruits and vegetables, is recommended.

To study the association between micronutrients, such as vitamins and selenium, and the development of cancer at a later date, the NCI is identifying banks of human blood samples that have been previously collected and frozen and can be related to individual cancer incidence. Inherent in epidemiological studies of this type and in human intervention trials are hidden factors that may confuse interpretation. To reduce one potential bias, analytical error, DRCCA is planning to support a clinical chemistry and quality assurance center that will standardize the measurement of micronutrients in fresh and frozen blood for NCI-sponsored human trials.

In 1971-1975, the National Center for Health Statistics collected dietary and health information from a representative sample of about 23,000 Americans for the first comprehensive National Health and Nutrition Examination Survey (NHANES I). The National Center for Health Statistics, in cooperation with several institutes of the National Institutes of Health, including the NCI, is now conducting an extensive epidemiological followup of the approximately 15,000 adults examined in NHANES approximately 10 years earlier. The NCI objective is to determine whether diet and nutrition are associated with cancer at specific sites through the collection of cancer incidence and mortality data on these individuals.

The Chemoprevention Program also will include studies of chemopreventive agents in persons at high risk for certain types of cancer, and the development of synthetic compounds for these clinical studies.

The group of potential chemopreventive agents currently being studied includes the naturally occurring substances: vitamins A, C, E, beta-carotene, and selenium. Synthetic retinoids are also being investigated. Laboratory, animal, and epidemiological studies, and clinical trials on these substances are described below.

I. VITAMIN A

NCI's early chemoprevention research was concerned mainly with vitamin A and its derivatives, the retinoids. These substances continue to be a major thrust.

A. Laboratory and Animal Studies

In 1955, Ilse Lasnitzki, of the Strangeways Research Laboratory in Cambridge, England, showed that precancerous changes in mouse prostate cells treated with the carcinogen methylcholanthrene could be inhibited by vitamin A. More recently, NCI investigator Michael Sporn and his coworkers, in collaboration with Richard Moon and colleagues, of IIT Research Institute of Chicago, showed that feeding rats and mice 13-cis-retinoid, a synthetic retinoid, inhibited the development of carcinogen-induced bladder tumors in these animals. These researchers also demonstrated that carcinogen-induced rat mammary tumors could be reduced to as low as one-fifth the expected incidence by feeding synthetic retinoids after carcinogen exposure. Roswell K. Boutwell and his colleagues at the University of Wisconsin have shown that giving synthetic retinoids inhibits the later (promotion) stage of skin cancer development in mice.

These are only a few examples. Other laboratory and animal data indicate the potential of retinoids in preventing or reversing the uncontrolled, disorderly growth characteristic of the later stages of cancer formation.

Natural retinoids are known to have toxic effects in animals, particularly at high doses. Researchers now are trying to develop synthetic retinoids that are as effective as natural retinoids in inhibiting tumor growth, are less toxic, and are more site-specific. They also want to understand how these inhibitors work in the later stages of cancer formation.

B. Epidemiological Studies

Studies in Norway showed that smokers who consumed low amounts of vitamin A had a somewhat higher lung cancer risk than those who consumed adequate amounts of vitamin A. Carrots, milk, and eggs were the main source of vitamin A in these subjects. Studies confirming this observation have been reported in the United States also.

Richard B. Shekelle and colleagues in Illinois suggest that the benefit may be related more to the dietary beta-carotene precursor than to vitamin A itself. About 20 questionnaire studies suggest an inverse association between vitamin A or beta-carotene intake and various types of human cancer.

In two studies measuring retinol (vitamin A) levels in frozen blood sera, individuals who later developed cancer had lower retinol levels than a comparison group who did not develop cancer.

NCI-funded Studies. Two epidemiological studies have been designed to test the relationship between lung cancer risk and vitamin A ingestion. Dr. Laurence N. Kolonel, at the University of Hawaii at Manoa in Honolulu, is assessing vitamin A intake in 500 lung cancer patients, and in 1,000 age- and sex-matched healthy volunteers. A second study conducted by Dr. Alfredo Lopez, at the Louisiana State University Medical Center of New Orleans, was completed in August 1982. He compared vitamin A intake of healthy volunteer with that of living patients with lung cancer, and, by interviewing their families, with that of lung cancer patients who have died. Since the

preliminary findings suggest that beta-carotene may have a more significant inverse association with lung cancer incidence than vitamin A, these results will be discussed in the section on beta-carotene (pages 5-6).

C. Clinical Trials (NCI-funded)

Some groups at high risk of cancer are taking part in several Phase I trials on chemopreventive agents that are designed to assess toxicity, safe dosage levels, and best dosage schedule.

These high-risk groups include patients with conditions that may be precancerous, among them cervical dysplasia (abnormal cell formation in the cervix or neck of the uterus); leukoplakia (potential precancerous patches in the mouth); familial polyposis (a condition predisposing to colon cancer); and certain skin disorders.

Two NCI-funded retinoid trials aimed at preventing cervical dysplasia are in Phase I studies to determine safe doses.

Dr. Frank L. Meyskens, of the University of Arizona Health Sciences Center in Tucson, has determined the safe dosage level for the vitamin A derivative, all-trans-retinoic acid, in women with cervical dysplasia. The agent is in gel form, embedded in a collagen sponge within a cervical cap that is applied by a physician. Dr. Meyskens is about to begin another Phase I trial using retinyl acetate, another retinoid, with the same application technique.

Another Phase I retinoid trial for cervical dysplasia is being conducted by Dr. Seymour Romney at the Albert Einstein College of Medicine, in the Bronx, New York. In this study, the patient at risk for cervical cancer applies a retinyl acetate gel to her cervix using a vaginal applicator.

These Phase I trials will be followed by double-blind studies to compare the cancer-preventive effect of these retinoids with a placebo.

Dr. Gary L. Peck, of NCI's Dermatology Branch, has shown that the synthetic retinoid 13-cis-retinoic acid may be of value in the treatment and the prevention of basal cell carcinoma, a skin cancer. Patients with this cancer are prone to the development of multiple new skin cancers.

II. BETA-CAROTENE

Beta-carotene is a common dietary source of vitamin A. The beta-carotene derived from leafy, green and yellow vegetables is converted to vitamin A in the digestive tract. It is uncertain whether only beta-carotene's conversion to vitamin A or other factors as well are involved in its association with reduced cancer risk.

Beta-carotene is not as toxic as vitamin A. In animal and limited Phase I human studies, it has shown no toxicity. The dose proposed for human chemoprevention trials is substantially lower than the upper limits used in these Phase I trials.

A. Laboratory and Animal Studies

Very little has been published in the scientific literature on the modifying effects of beta-carotene on induced tumors. Some of these studies have shown that beta-carotene may protect against chemically induced skin cancers and against skin cancers induced by ultraviolet rays. These findings are reviewed by Richard Peto and colleagues at the Imperial Cancer Research Fund in Oxford, England, the University of Oxford, and the NCI, in Nature, vol. 270, pp. 201-208, 1981.

B. Epidemiological Studies

Many epidemiological studies have reported a relationship between beta-carotene and cancer. Dietary questionnaires designed for more general purposes happened to ask about the main beta-carotene source and an association between lower cancer risk and users of foods high in beta-carotene was realized only later. Although the evidence thus far available is not compelling that beta-carotene is truly protective against cancer, it seems unlikely that this question will be decided in the foreseeable future unless controlled human trials are undertaken. The lack of toxicity of this substance in animal and limited Phase I trials justifies its use in clinical trials.

Drs. Regina Ziegler, Thomas Mason and coworkers in NCI's Environmental Epidemiology Branch, in collaboration with the New Jersey Department of Health and the University of Texas School of Public Health, are conducting a study to assess the relative contributions of vitamin A and beta-carotene in reducing the risk for lung cancer. The scientists are comparing vitamin A with beta-carotene intake by interviewing living patients with lung cancer, close relatives and friends of patients who have died with lung cancer, and normal people of comparable age, race, and sex, in certain areas of New Jersey and the Gulf Coast of Texas, where lung cancer death rates are higher than in the U.S. as a whole.

Dr. Alfredo Lopez, of Louisiana State University Medical Center, New Orleans, has conducted two case control studies on lung cancer and vitamin A. One study compared vitamin A and beta-carotene stored in the liver of patients who had died of lung cancer with stores of those substances in three control groups: (1) patients with no diseases who had died from accidental causes; (2) patients who had died from cancers other than lung cancer; and (3) patients who had died in hospitals from diseases other than cancer. The most significant difference was found between lung cancer patients who had died and healthy people who had died from accidental causes. Those who had died of lung cancer had the lowest levels of vitamin A and beta-carotene in the liver.

Dr. Lopez also conducted a study of living patients with lung cancer. Compared with healthy volunteers of comparable age, race, and sex, the lung cancer patients had lower serum levels of vitamin A and beta-carotene. In interviews regarding their vitamin A intake, lung cancer patients' responses indicated their vitamin A intake to be higher and their beta-carotene intake lower than those of the healthy volunteers. Although high vitamin A intake and low serum level of vitamin A may appear contradictory, these data may be compatible if vitamin A intake is expressed as the

retinol equivalent. The retinol equivalent consists of (1) beta-carotene, a vitamin A precursor in leafy, green and yellow vegetables that is broken down into vitamin A in the body, and (2) preformed vitamin A, or retinol, present in pill form and certain foods. Expressed as a composite of preformed vitamin A and beta-carotene per 1,000 kilocalories eaten, the vitamin A intake is lower for lung cancer patients, who take in less beta-carotene than healthy volunteers. These findings suggest beta-carotene may be as important or possibly more critical than preformed vitamin A in minimizing the risk of lung cancer.

C. Clinical Trials (NCI-funded)

A cooperative clinical trial has begun with 60 percent funding by the National Heart, Lung and Blood Institute and 40 percent by NCI, to test the potential of beta-carotene in lowering cancer incidence and of aspirin in reducing mortality from cardiovascular disease. Dr. Charles Hennekens, of Harvard Medical School and Brigham and Women's Hospitals in Boston, began the study in the fall of 1981. Some 20,000 healthy U.S. male physicians over 40 years of age are expected to participate. They will be divided into four treatment groups, of about 5,000 each. Group 1 will receive aspirin and beta-carotene on alternate days; group 2 will receive aspirin and placebo on alternate days; group 3 will receive placebo and beta-carotene on alternate days; and group 4 will receive placebo every day.

The study will examine: (1) if aspirin reduces the mortality from cardiovascular disease (earlier studies, when examined in aggregate, showed that aspirin reduces the rate of reinfarction by 21 percent and mortality from cardiovascular disease by about 16 percent among patients who have already suffered a myocardial infarction); (2) if beta-carotene contributes to a decrease in total cancer incidence in this group; and (3) if aspirin and beta-carotene interact in any way.

NCI is also conducting a clinical trial to test the findings of animal studies that showed that beta-carotene protected against skin cancer induced by ultraviolet light. This trial will be conducted by Drs. Gideon Luande, of the Muhimbili Medical Center in Tanzania, East Africa, and Claudia Henschke, of Brigham and Women's Hospitals, Boston. The population at risk in this trial is a group of albino Africans in Tanzania who often die from skin cancer before age 30. These people lack the skin pigment that protects against the intense solar radiation near the equator. It is hoped that an oral mixture of beta-carotene and canthaxanthin, a substance with the cosmetic benefit of bronzing the skin, will protect them.

III. VITAMINS C AND E

Vitamins C and E appear to prevent the formation of nitrosamines or nitrosamides, potential carcinogens resulting from metabolic reactions in the human digestive tract of nitrates, nitrites, and substances readily found in foods.

Nitrosating agents react with amines or amides in the digestive tract to form nitrosamines and nitrosamides; respectively. These agents include nitrite salts, such as sodium nitrite, added to meat for color, flavor development, and control of bacterial contamination; nitrate salts, used in

food processing, that are readily reduced to nitrite in the living person; fermentation processes, such as pickling or brewing, that permit conversion of a variety of nitrogen sources, including ammonia, amino acids, etc., to nitrite; and nitrogen oxides derived from "smoking" processes.

Vitamins C and E compete with the amine or amide for the nitrosating agent. If the vitamin "wins," reacting with the nitrosating agent, the formation of nitrosamines and nitrosamides is blocked.

Vitamin C is present in many fruits and vegetables and in dairy products. In these forms, it can be safely taken in large amounts over long periods of time. Further study is required to determine a maximum safe dose level for the vitamin supplement forms.

Vegetable oils are the richest dietary sources of vitamin E and it is abundant in other foods. Vitamin E, or alpha tocopherol, may inhibit cancer development by quenching highly reactive forms of compounds in the digestive system.

There are limited studies on the long-term side effects of alpha tocopherol. Findings indicating that vitamin E may have unfavorable effects in pregnant women are only preliminary and require further study.

A. Animal and Laboratory Studies

Laboratory and animal studies show that vitamin C blocks the formation of nitrosamines. Massive doses of vitamin C have completely protected rats against chemically induced liver tumors and have partially protected them from lung and kidney tumors.

Vitamin E has been reported to reduce the incidence of chemically induced tumors of the colon in mice.

B. Epidemiological Studies

1. Vitamin C

Epidemiological studies suggest that lettuce and other vegetables containing vitamin C may offer specific protection for the upper digestive tract.

Studies in northern Iran suggest that dietary constituents or deficiencies may be responsible for the high incidence there of cancer of the esophagus and, more specifically, that diets very low in fresh fruit and vegetables may contribute to cancer of the esophagus. [Joint Iran-International Agency for Research on Cancer Study Group, 1977; Cook-Mozaffari et al., 1979]

Dietary constituents or deficiencies have also been suggested to contribute to the incidence of cancer of the esophagus in certain provinces in China. Similar factors have been implicated for the high incidence of stomach cancer in Colombia and Chile.

Changes in cancer incidence associated with diet modification have been reported in studies of Japanese from areas with high stomach cancer risk who migrate to Hawaii. Although the migrants continued to have a high risk in Hawaii, this stomach cancer risk was lower among their offspring born in Hawaii. Some investigators suggest that the Western-style diet, including foods rich in vitamin C, may have contributed to this lowered risk.

2. Vitamin E

Epidemiologic data concerning the protective effect of vitamin E on cancer are scarce. It has been shown in normal human stool that vitamins C and E reduce the level of agents, known as mutagens, that induce gene changes. Whether these agents can prevent or postpone recurrence of potentially cancerous polyps in the colon is being investigated in clinical studies of groups at high risk of developing colon cancer.

C. Clinical Trials

1. Not Funded by NCI

Canadian researcher W.R. Bruce and colleagues, at the Ludwig Institute for Cancer Research in Toronto, are conducting a double-blind study to evaluate the protective effects of vitamins C and E in lowering the recurrence rate of potentially cancerous lesions of the colon known as polyps.

Robert London and G.S. Sundaram, at Sinai Hospital in Baltimore, Maryland, have shown that vitamin E is effective in reducing the clinical symptoms of fibrocystic disease of the breast; i.e., lumpiness, size and number of cysts, pain, and tenderness. The relevance of these studies to breast cancer is unknown at this time.

2. NCI-funded Clinical Trials

Basil C. Morson and coworkers, of St. Mark's Hospital in London, in collaboration with Dr. Jerome DeCosse of New York's Memorial Sloan-Kettering Cancer Center (MSK), have reported the results of a human study to examine the potential use of vitamin C in preventing cancer of the large bowel. The trial results were reported in the October 1, 1982 issue of Cancer, volume 50, pages 1434-1439. Patients with familial polyposis, an inherited disorder characterized by polyps, were treated after surgical removal of affected parts of the colon, either with large oral doses of ascorbic acid or with a placebo. The trend toward reduction of rectal polyp growth in the ascorbic acid-treated group suggested a need for further studies of this effect.

Dr. Steven R. Tannenbaum, of the Massachusetts Institute of Technology (MIT) in Cambridge, is evaluating various dietary factors that may prevent nitrosamine formation. To date, about 12 healthy volunteers in the MIT trial have received vitamin C and the vitamin has blocked nitrosamine formation as measured by a reduction in their urine nitrosoproline concentrations. A similar trial using vitamin E is in progress.

IV. SELENIUM

Seafoods, organ meats, and some grains are rich in selenium. Intake varies in different populations because of soil content and the amount of meat eaten. Much of the selenium in the body and blood may not be physiologically active.

Although selenium is an essential element, chronic selenium poisoning may result from selenium overdosing through abuse of nutritional supplements.

A. Animal and Laboratory Studies

Laboratory studies have indicated that certain forms of selenium modify enzyme activity that may possibly be related to cancer inhibition. Dr. Carmia Borek of Columbia University has reported that selenium may "protect" against radiation- and chemical-induced cancer in cells grown in the laboratory. Selenium also can reduce induced mutation rates in bacterial tests. Further research is needed to confirm these and other studies concerning inhibition of cancer formation in laboratory-grown cells.

Numerous animal experiments have shown that selenium has an antitumor effect. The relevance of most of these studies to cancer risk in humans is not clear since the levels of selenium used far exceeded recognized dietary requirements and often approached toxic levels. However, one experiment has shown that selenium deficiency and high levels of dietary polyunsaturated fats increases susceptibility to chemically induced tumor formation, while a dietary supplement of selenium close to the physiological requirement offers protection. The role of dosages in the broad range between the apparently nutritionally adequate and the higher, effective level used in many antitumor studies has not yet been adequately investigated. The incidence of chemically induced colon cancer and liver tumors in rats can be reduced by adding certain forms of selenium to the drinking water. There is sufficient evidence to warrant further research on the antitumor effect of selenium.

B. Epidemiological Studies

The epidemiological evidence pertaining to the relationship between selenium and cancer is derived from a number of geographical correlation studies that associate cancer risk with estimates of individual selenium intake, with selenium blood levels, or with selenium concentrations in the water supply or soil. In the northeastern United States, high colon, rectal, and breast cancer rates have been correlated with low soil selenium. In most areas studied, there is an inverse relationship between selenium level and cancer. However, it is not clear whether this relationship applies to all cancer sites or only to specific ones, such as the digestive tract. Rigorous epidemiological studies of selenium and cancer have not been reported, and the effects of dietary selenium supplements on subsequent cancer development have not been demonstrated.

Data related to selenium intake are being gathered now in studies in China, Finland, and other countries where people are receiving selenium supplements or have low selenium intakes.

V. BROAD STUDIES (NCI-funded)

Pelayo Correa, of the Louisiana State University Medical School in New Orleans, has been collaborating with Steven R. Tannenbaum, of MIT, and Martin Lipkin, of MSK, on studies correlating levels of vitamins A, C, E, and beta-carotene with precursor conditions in the stomach that may lead to cancer. Two populations at high risk for stomach cancer are being studied: one in Marino, Colombia, and a group of black patients at the Louisiana State University Medical School Gastrointestinal Clinic.

The individuals in Marino, Colombia, answered questionnaires about their diet at the start of the study and will be interviewed again four to five years later. Blood samples have been drawn to assess levels of vitamins A, C, E, and beta-carotene. Parameters for precursor conditions were based on samples of tissue (biopsies), gastric juice, and urine. Nitrosamine formation is being evaluated from tests of their gastric juice. The expression of fetal antigens in the cells of their biopsy specimens are being evaluated as possible indicators of a precancerous stage.

As was done with the Colombian group, the diet questionnaires answered by the black patients in Louisiana will be correlated with the parameters studied in their biopsy, gastric juice and mucosa, urine, and blood samples. These correlations may provide useful insights for future intervention studies in cancer prevention.

A study to investigate the association of several dietary factors with decreased risk for certain cancers is being conducted by scientists in NCI's Environmental Epidemiology Branch. The stimulus for this research came from the U.S. maps of cancer mortality, based on data collected between 1950-1969 and published by NCI in 1975 and 1976, showing that death rates from colon, rectal, and breast cancers are about 50 percent lower in the south than in the northeast and north-central United States. Despite the large number of northerners who retire to Florida, this area retains the low rates of the south, even among older people. This observation suggests that the risk for colon cancer can be reduced by environmental influences.

These NCI scientists have also reported that the increased risk for cancer of the esophagus among black males in Washington, D.C., is associated with generally poor nutrition. Low intake of vitamin A or C, beta-carotene, thiamin, or riboflavin is a risk factor, independent of the effect of the even greater risk factor of alcohol consumption. Dietary information was obtained from interviews of relatives or close friends of black men who died in Washington, D.C., of esophageal cancer and of black men who died of other causes during 1975-1977.

NCI-funded studies examining numerous dietary and other risk factors, including the interaction of social and behavioral factors, are being conducted by Dr. Saxon Graham, State University of New York at Buffalo. This interdisciplinary research should provide analyses of numerous factors that may be associated with cancer prevention.

The studies described above are only the beginning. As preliminary findings from these research projects become known, future trials will be developed. Such efforts are already under way.

